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WILLIAM WITHERING—A BICENTENARY TRIBUTE

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AS A YOUNG, 23-year-old student at Edinburgh University, Withering wrote in a letter to his parents, in 1764, that the teacher of botany annually awarded a gold medal to encourage the best among his pupils. This led to great competition among the young men, "though," continues Withering, "I confess, it will hardly have charm enough to banish the disagreeable ideas I have formed of the study of botany." And yet, remarkably enough, it was as a botanist that he was to become famous and honored, and it was in the capacity of both doctor and botanist that he was to write his famous paper on the medical use of digitalis.

Withering was born March 28, 1741, at Wellington, in the Midlands. His father was a respected and much-sought-after doctor, and his mother came of an old, well-known medical family. They had three children. Withering's school career and upbringing were in no way remarkable. He learned the elements of the classics, mathematics, geography, and history, from a clergyman in the neighborhood. He did not distinguish himself in any respect either during this period or during his earlier years at the University. It was his father's wish that his son should become a doctor, and this was in conformity with Withering's own plans for his future.

At the age of 21 he began to study at the University of Edinburgh. He appears to have got on well there from the very first, as is seen clearly from his letters to his parents. At that time there were several prominent men among the teachers at the University, of whom Monro primus was the leading one. Withering pursued his studies, but also took part in social life; he had literary interests, he played golf, and he was musical and learned to play both the bagpipes and the flute. While he was still a student, Withering gave several short lectures on, *inter alia*, rachitis, angina inflammatoria, and dropsy, before the Medical Association in Edinburgh.

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In the spring of 1766 Withering graduated at Edinburgh, after four years' study, with a treatise entitled "Malignant Putrid Sore Throat." It was written in Latin and dedicated to his maternal uncle, Dr. Brooke Hector, and his first teacher, Henry Wood. As far as can be judged, Withering was at home in that language—he was a member of a Latin club at Edinburgh—but he was never a prominent Latin scholar. In this connection it may be mentioned that, with reference to another language, namely, French, Withering once wrote as follows: "I deem it a heavy task, during the short space of our existence, to be compelled to learn so many signs to indicate the same thing." Like many of the better situated young men of the time, Withering wanted to travel before settling down as a doctor, and he set off with a friend to France. The journey came to an abrupt end, however, for the friend, who was already ailing—probably a victim of tuberculosis—died suddenly; and, after all kinds of difficulties, caused, among other things, by a deficient knowledge of the language, Withering was compelled to return home. He had had time, however, to obtain a lasting impression of Paris, where he had visited hospitals and attended lectures.

The following Christmas Withering spent at home. He was now assisting his father, and, at the same time, he was beginning to look around for some suitable place where he could settle down as a medical practitioner. The doctor in the nearby little town of Stafford had recently died, and, as Withering had just successfully treated a prominent person who lived in the immediate vicinity, Stafford was thought to afford possibilities of a good start for the young man. A hospital for the poor had just been completed at Stafford, and Withering became its first doctor. He never built up a large practice during his time in Stafford, however, and thus his hospital duties and his private practice left a great deal of time on his hands. Withering belongs to the group of historical personages who developed slowly, later to present new and epoch-making ideas with all the greater force and penetration.

Passing by Withering's uneventful early years at Stafford, we find him, at the age of 30, a very busy man, in spite of his inconsiderable activities as a physician. He is studying botany.

In view of the above-quoted letter to his parents, in which he clearly announces his distaste for botany, it is undeniably surprising that it is just this subject that he studies voluntarily, devoting to it every leisure moment and all his energy. As far as the present author has been able to ascertain, there is nothing to indicate that his friend and fellow student Pulteney had any influence on Withering in this connection, but it is quite conceivable that such was the case. This Pulteney was a botanist, and wrote the first English biography of Linné. A more romantic circumstance—quite in keeping with the eighteenth century for the rest—undoubtedly contributed to directing Withering's interest particularly toward the English flora. One of his first patients in Stafford was a young lady, Helena Cooke, who was interested in flower paint-

ing. On his visits Withering used to bring with him flowers which he had picked himself. The young lady subsequently became his wife. There are many descriptions of how it became a habit of Withering's to collect plants and "curious stones" during his long rounds on horseback or by carriage.

Withering married in 1772, and in 1775 he moved to Birmingham to increase his practice and his income. His eldest son, who died in infancy, was born in Stafford, and his daughter Charlotte and his son William were born in Birmingham.

Broling, a Swede, wrote a "Journey to England," in which there is an excellent description of the flourishing industrial town, and also of the forceful and enterprising magnate Boulton, who became Withering's friend and patron. The person who really suggested to Withering that he should move to Birmingham was Dr. Erasmus Darwin, an uncle of the famous Charles Darwin. The suggestion was inspired by kindliness, but when Withering's reputation, both as a doctor and a scientist, began to eclipse Darwin's own, this good will was succeeded by persecution and petty annoyances which pained Withering very much. I shall return to this matter in connection with Withering's digitalis investigations.

In Birmingham Withering was appointed physician-in-charge at the hospital. He established an outpatient department, and on certain days of the week his private consultations were also open to poor persons. His practice grew rapidly, and in his second year there he earned as much as during his whole eight years at Stafford, but, at the same time, the first evidence of the silent toil of past years presented itself. In 1776 there appeared the first edition of his well-known botanical work, "A Botanical Arrangement of all the Vegetables naturally growing in Great Britain, with Descriptions of the Genera and Species, according to the System of the celebrated Linnaeus." Withering gave a detailed description of each plant, and he sums up thus: "Under each species are added the most remarkable Varieties, the Natural Places of Growth, the Duration, the time and Flowering, the Peculiarities of Structure, the common English Names; the Uses as Medicines, or as Poisons, as Food for Men, for Brutes and for Inseckts;" and he adds: "With their Applications in Oeconomy and in the Arts." In his preface, in which he goes through all the different points, Withering remarks that many people will doubtless be surprised that he has said so little about the medical uses of the plants. But he considers that they have been abused in this respect, and that superstitious beliefs have led to the use of all sorts of plants for the most varied diseases. On the other hand, he points out that valuable remedies can be prepared from plants. Nothing can better illustrate Withering's own starting point and the contribution he made, as a result of his own investigations into the effects of digitalis, than what he himself wrote in the first edition of his Flora. "Certain Plants, capable of producing very sudden and remarkable

effects upon the Human Body, are called Poisons. But poisons in small doses are the best medicines, and the best medicines in too large doses are poisonous.'' Under Foxglove, i.e., digitalis, in the same flora, we find the following remark: ''A dram of it taken inwardly excites violent vomiting. It is certainly a very active medicine, and merits more attention than modern practice bestows upon it.''

How extensive Withering's practice in Birmingham was, appears from a statement that during one year—1785—his visits to the sick involved travelling more than 6,353 English miles. He made these journeys, which were an extremely great strain at that time, on horseback or by carriage. In order to employ every moment, he had ''a light'' in his carriage—presumably an oil lamp—so placed that he could read and study during his journeys. Withering's activities as a doctor comprised both those of the hospital doctor and of the very popular practitioner, but yet he found time not only for medical studies, but also for profound botanical, chemical, and mineralogical studies. The period in Birmingham can probably be characterized as the most active period in this ever active man's life.

In 1779 he published a work entitled ''An account of the Scarlet Fever and Sore Throat.'' In the preceding year there had been a severe epidemic of scarlatina in Birmingham, and the disease had also ravaged the whole of England. Withering hoped—as he says in his preface—that his observations would be of use. Scarlatina was often confused with other illnesses. The book attracted much attention in its time. During these and the immediately succeeding years, Withering published several nonmedical papers, *inter alia,* in 1783, an English translation of the Swedish mineralogist Torbern Bergman's ''Sciagraphia Regni Mineralis.''

At this time there was an illustrious society in Birmingham, the ''Lunar Society,'' of which Withering was elected a member. Through a Mrs. Schimmelpenninck, whose father was also a member of this club, we have very graphic descriptions of the meetings of the club and of its members, among whom—besides its celebrated chairman, Dr. Samuel Johnson—were the Boulton referred to previously, James Watt, the inventor of the steam engine, Joseph Priestley, the English discoverer of oxygen, and the Dr. Erasmus Darwin mentioned above. Many famous men visited the club, *inter alia,* the Swede Solander—Linné's pupil—and Benjamin Franklin. Priestley was a close friend of Withering's and the latter interested himself very much in the new and much discussed discoveries announced by Priestley. He was convinced that Priestley was right, and defended his friend both in speech and writing.

In 1785 Withering was elected a member of the Royal Society, in whose Transactions he published several of his works. In the same year he was also awarded a diploma by the Medical Society of London, and was subsequently (1791) elected to the Linnéan Society. Otherwise he declined the membership of clubs and societies, since, as always, he was

concentrating his time and energies on his work. It was in 1785, also, that he published his work on digitalis, "An account of the Foxglove, etc.," to which I shall devote special attention below.

Withering's reputation, both as a research worker and as a doctor, was now at its zenith. The French botanist, L'Héritier de Brutelle, named a plant *Witheringia solanacea* in his honor. Birmingham was an interesting town in many respects, and to it went many of the foreigners who visited London. Withering's son gives a list of tourists and scholars from Germany, France, Holland, Poland, and Sweden who visited his father, and with whom the latter often carried on a voluminous correspondence.

As early as 1776, Withering had himself noticed the first symptoms of the disease—probably pulmonary tuberculosis—which was to be the cause of his death. Every winter subsequent to that date he had attacks of varying severity. In the winters of 1783 and 1784 he had to give up his practice for long periods and take a complete rest in the country. This is the real reason why, in 1786, he realized his desire to move to the country. He settled down at Edgbaston Hall, outside Birmingham. Nowadays the beautiful hall lies in a suburb of Birmingham, but in Withering's time the district could quite justifiably be described as the country. It was not too far from the town, however, for him to be able to continue to carry on his daily work as a doctor.

At Edgbaston Hall Withering was able, in some degree, to live the country life he had longed for so long. He was interested in the management of the estate, and took a special interest in rearing Newfoundland dogs. Among his pets there were also two monkeys from Gibraltar. One of them died after a few years. Withering followed the monkey's illness carefully—coughing, fever, and wasting. According to Withering, the autopsy revealed "Phthisis pulmonalis similar to that found in human victims." This comment was probably made principally with himself in mind. In 1790 he had an unusually severe pulmonary attack. He began to suffer from breathlessness, and his fatigue made itself felt more and more, but his will to work was still unbroken. He continued many of his works, and to a certain extent carried on his practice. How he suffered because of the feeling that his strength was failing is seen plainly from an utterance quoted by his son in Miscellaneous Tracts: "The languor of illness is one of the most mortifying symptoms to those who dislike indolence."

The results of the political unrest which spread to England from revolutionary France contributed indirectly to Withering's failure to improve. Both as a doctor and a private citizen, Withering remained entirely outside political discussions and belonged to no party. His home was threatened during serious riots in Birmingham in July, 1791. Withering tried to save his library and his scientific collections by removing them in wagons loaded with hay. Even though damaged, both

his collections and his home escaped destruction, to which his popularity as a doctor certainly contributed, but the severe mental strain weakened his health further.

Portugal was a holiday resort much favored by Englishmen, especially during the winter, when they wanted to escape from the cold, damp climate of England. In September, 1792, Withering went to Lisbon. During the winter there his health improved to such an extent that he repeated the journey the following year, but not with the same good result. On the contrary, he returned with his strength further reduced. In Portugal Withering studied the subtropical flora and also made water analyses, especially of the hot springs at Caldas da Rainha. His work was published by the Royal Academy in Portugal, of which he was elected a corresponding member. In this connection it may be mentioned that he had already previously—in 1776— translated into English T. Bergman's "De Analysi Aquarum."

Although Withering never had an opportunity of visiting Sweden, he not only met several Swedes, but also cooperated for long periods with Adam Afzelius and Carl Peter Thunberg. Letters are still preserved from the lively correspondence he kept up with these two Swedish botanists. They contributed to a great extent to the working up of the third, much larger edition, of Withering's "Botanical Arrangement," which appeared in 1796 (a quotation from Thunberg appears on the flyleaf).

After his return from the last journey to Portugal, Withering spent most of his time in his library, which he tried, by means of various contrivances, to keep at a constant temperature of about 18° C. In spite of everything, however, Withering was more and more troubled by breathlessness, and at times he had hardly strength to sit writing at his desk. He began to think that Edgbaston Hall, where he had always been so happy, was unsuitable on account of its exposed position, and decided to move to Dr. Priestley's former home. He had the house, which had been almost entirely destroyed by revolutionaries during the period of unrest, carefully repaired.

He never found the relief which he had hoped for so much. On September 28 he moved to his new home, "The Larches," but only eight days later he passed away, on October 6, 1799.

Withering was buried in the old church at Edgbaston. On the tablet of black marble, in addition to the name and particulars, a poem was engraved in the taste of the period, but on the base of the tablet Withering's work is symbolized better than by many words. The emblem of Aesculapius, the serpent-wreathed staff, is sculptured, surrounded by flowering digitalis and *Witheringia solanacea,* cut from living specimens.

Withering's most lasting contribution was undoubtedly his fundamental work on the use of digitalis as a remedy, and therefore that work will be dealt with in detail.

The use of digitalis as a medicinal plant can be traced both among the Irish monks and in Germany, where it appears to have been cultivated as early as in the time of Charles the Great. In 1546 a drawing of it was made by Hieronymus Bock. Leonhard Fuchs gave it its Latin name. After Fuchs' time there are no particulars of its use in German-speaking countries up to Withering's days. On the other hand, in England it was mentioned occasionally before his time (Gerarde, 1597, Parkinson, 1640), and it was used as a remedy for illnesses of the most varied kinds, such as epilepsy, sores, swellings, and vertigo. Digitalis was included in the London pharmacopoeia in 1650.

That the knowledge of digitalis was confined especially to England may be due to the fact that it is a very common flower and grows in great profusion there.

As is well known, Withering was a skilled and meticulously observant physician, as well as a learned botanist. In his book "An Account of the Foxglove, and some of its Medical Uses, with Practical Remarks on Dropsy," he describes how his interest in digitalis was first aroused. In 1775 he was questioned about an old prescription for the cure of "dropsy" with which "an old woman" in Shropshire was said to perform miracles after doctors had failed. The old woman's prescription proved to be compounded of twenty different herbs, but it was not difficult for Withering—as he says himself—to discover that digitalis was the effective ingredient. It had been used as an emetic and a laxative, but its influence on the heart and its diuretic effect had clearly not even been noticed. In the preface to his book, Withering says quite modestly that he had often been urged to write about digitalis, and equally often had refused to do so, but finally, with hesitation—however incompetent he felt himself—he had decided to take up his pen. What really led to Withering's publication was as follows, as he expresses it himself: "The use of the Foxglove is getting abroad, and it is better the world should derive some instruction, however imperfect, from my experience, than that the lives of men should be hazarded by its unguarded exhibition or that a medicine of so much efficacy should be condemned and rejected as dangerous and unmanageable." Ten years' experience with digitalis as a diuretic, tested on a comprehensive material, comprising 163 of his own cases of "dropsy" and the experiences of various doctors, forms the basis of Withering's classic work, in which he presents his results with extreme objectivity. Case after case is described in the most concise form possible, with the histories and physical signs, and with day-to-day notes on the effects of the drug. In many cases its diuretic effect was extremely striking. Only a few days' use of the remedy was sometimes sufficient to cause the edema to disappear. In other cases of dropsy, again, results were insignificant or completely absent. If the histories of the different patients are studied, it will be found that, as a rule, Withering succeeded in getting the diuresis started in the cases in which there were both edema and asthma, i.e., difficulty

in breathing during rest or on exertion; in other words, in cases of what we usually call chronic cardiac insufficiency. Withering gives particulars of only one case from the year 1775. After 10 days' treatment with a decoction of digitalis, large quantities of water had been excreted, the difficulty in breathing had receded, and the general condition was improved.

From the following year he reports four cases, of which No. IV is remarkable in several respects, and is given in detail here. On July 25, 1776, Withering was consulted by Dr. Erasmus Darwin—the older colleague who had advised Withering to move to Birmingham—about one of Darwin's patients. A middle-aged married woman was suffering from extremely troublesome dyspnea; her pulse was weak and irregular, her arms cold and clammy. She had troublesome orthopnea and could not lie down in bed. She had considerable edema in her legs, thighs, and over the abdomen, and passed extremely small quantities of urine. It had been proposed to scarify her legs but the proposition was not acceded to. Dr. Darwin had tried, *inter alia,* antispasmodics, diuretics, and laxative remedies, without result. Withering then pointed out: "In this situation I knew of nothing likely to avail us, except the Digitalis: but this I hesitated to propose, from an apprehension that little could be expected from any thing; that an unfavourable termination would tend to discredit a medicine which promised to be of great benefit to mankind, and I might be censured for a prescription which could not be countenanced by the experience of any other regular practitioner. But these considerations soon gave way to the desire of preserving the life of this valuable woman, and accordingly I proposed the Digitalis to be tried; adding, that I sometimes had found it to succeed, when other, even the most judicious methods, had failed. Dr. Darwin very politely acceded immediately to my proposition, and, as he had never seen it given, left the preparation and the dose to my direction." Fol. Digitalis was prescribed; within twenty-four hours diuresis started, and 9 liters of urine were excreted. An appreciable general improvement set in, the dyspnea was relieved, the pulse became stronger and more regular, and the edema in the legs disappeared. After that Darwin and Withering looked after the patient alternately until September 10, when Withering took her over entirely. Nine days later, on September 19, the edema had begun to return, and another course of digitalis was begun, with the same brilliant results as on the first occasion. At the end of his description Withering says that he attended this woman for nine years, and gave periodical courses of digitalis which obviously prevented the edema from developing to any more appreciable extent. He adds that, for this, "very small doses" are required. The case illustrates the almost miraculous effect of digitalis. The remedy not only saved this woman's life in the more acute stage, but in small doses it kept her alive for nine years, and prevented edema. Our conception of its value as a therapeutic agent in the treatment of

chronic cardiac insufficiency has not changed to any considerable degree since Withering's days. The following lines by Withering, which conclude the description of this case, are of very special interest: "I have been more particular in the narrative of this case, partly because Dr. Darwin has related it rather imperfectly in the notes to his son's posthumous publication, trusting, I imagine, to memory, and partly because it was a case which gave rise to a very general use of the medicine in that part of Shropshire."

According to Professor John Fulton, of Yale University, who attemped to elucidate the priority as regards the discovery of the therapeutic value of digitalis, Erasmus Darwin's formal priority is clear, for, in an addendum to his son's doctor's dissertation, he published as early as 1780 an account of some patients with "dropsy" who were successfully treated with digitalis. In January, 1785, he published in Medical Transactions his second study on the subject. Withering's "Account of the Foxglove" is dated in July of the same year. However, Darwin's procedure in this matter can be looked upon as none too punctilious according to modern conceptions, for Withering's description, as given above, is considered fully verified, and thus Darwin learned about the effect of digitalis for the first time from Withering, in 1776. Withering's ethical priority is thus absolute.

In any case, the news of Withering's therapeutic successes with digitalis spread far and wide in England. He received large numbers of letters from colleagues, full of praise for his observations, and some of these letters are reproduced in his book.

Withering had not only collected an abundance of cases in which dropsy had been successfully treated, but had also made detailed studies of the purely botanical features of this remarkable plant, and in his book a beautiful colored reproduction of a specimen of digitalis, with its purple, bell-like flowers, appears. In a special chapter he gives advice as to the preparation of the drug. In the first place, the leaves should be collected just at flowering time and then dried. Withering prescribed that, as a rule, the leaves should be pulverized, and the medicine given in the form of an extract, infusion, or powder, as pills or tincture, but he says rightly: "But the more we multiply the forms of any medicine, the longer we shall be in ascertaining its real dose." With regard to the dosage, it is amazing how little Withering prescribed: "1-3 grains (0.12-0.36 gram) twice daily," which amount tallies extremely well with that used by doctors to this day. On the other hand, his predecessors, the quack doctors, used considerably larger, nay, dangerous doses, against which Withering gives a very special warning. As a drastic example of such overdosing, even by his colleagues, Withering mentions that a Dr. Cawley himself took twelve times the above-mentioned dose, but that he must have had an unusually strong physique, for otherwise he would have died of digitalis poisoning. Withering was very well acquainted with the symptoms of poisoning from digitalis, and

describes them in detail as follows: "The Foxglove, when given in very large and quickly-repeated doses, occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow, increased secretion of urine, with frequent motions to part with it, and sometimes inability to retain it; slow pulse, even as slow as thirty-five in a minute, cold sweats, convulsions, syncope, death." Withering advises a continuance of the proposed daily doses until the drug has affected either the kidneys, stomach, pulse, or intestines, but that it shall be discontinued as soon as symptoms from any of these organs make their appearance. From a study of Withering's book on digitalis, it appears clear that Withering undoubtedly discovered its strong diuretic effect; previously the drug had been known only as a laxative and emetic, probably because the medicine had been given in overdoses.

Withering sums up his conclusions on the diuretic effects of digitalis in eight points at the end of the book, but adds a ninth point which is particularly worthy of attention, and therefore I quote it here: "That it has a power over the motion of the heart to a degree yet unobserved in any other medicine, and that this power may be converted to salutary ends."

It was not sufficient that, during a period of ten years, Withering, with his extraordinary powers of observation and his critical penetration, established the fact that digitalis is above all an unsurpassed diuretic, but he also discovered its extraordinary effect on the heart and its movements. In a number of his case histories he remarks particularly that, during treatment with digitalis, the action of the heart becomes slower. Withering was the first to establish the specific effect of digitalis on the heart, an observation which modern physicians consider the most important and self evident. In Withering's time, "dropsy" was a morbid state in which digitalis was sometimes efficacious, and sometimes not, as he very correctly points out. Today it is known that dropsy is a symptom of different conditions, such as kidney diseases, diseases of the liver, and, especially, cardiac insufficiency, and that it is only with the latter form of dropsy that digitalis is a specific remedy because of its effect on the heart. Without being in a position to make this classification of dropsy, Withering describes—as has been pointed out above—cases of successfully treated dropsy, the symptomatology of which he describes with unusual acumen, and which in our time would be diagnosed as cases of typical cardiac insufficiency.

At first, Withering's digitalis treatment did not attract any considerable attention within the medical world. Neither Corvisart, Napoleon's court physician, nor his pupil, Laennec, devoted any great interest to digitalis, although they were among the outstanding figures in medicine, and for over fifty years digitalis was very little used as a cardiac medicine. In 1798, Hahnemann, the founder of homeopathy, spoke extremely skeptically and sarcastically about digitalis as a medi-

cine. It was the German clinicians—first, Kreysig, in 1814, and, subsequently, Ludwig Traube, in 1864—who became interested in the use of digitalis for heart disease. Traube established, in the first place, that digitalis had a regulating effect on the rhythm of the heart, and that it reduced the heart frequency. Leyden (1881) and Nothnagel (1878) arrived at the conclusion that digitalis was our foremost remedy for the treatment of cardiac insufficiency, and its clinical use was first elucidated by these research workers and their contemporaries, James Hope and William Stokes. The knowledge of digitalis was greatly widened by Homolle, Quevenne, and Nativelle, and, above all, by the fundamental work of Schmiedeberg, the German pharmacologist, in 1875. These investigators, in the first place Schmiedeberg, attempted to isolate the active substances, which were called glucosides, from the digitalis leaves. Later, all over the world, innumerable pharmacologists began to test these substances which affected the heart by means of experiments on animals, and established the principle for the pharmacologic effect of the so-called cardiac glucosides. Broadly speaking, the experiments on animals taught that digitalis evoked a stronger contraction of the heart muscle.

It might be said that full justice had not been done to Withering's pioneer work until during the last fifty years. Clinicians in all countries now see in digitalis the pre-eminent heart remedy, which has the power to relieve cardiac insufficiency and strengthen the failing heart; which in countless cases actually performs miracles, and helps persons with heart disease of various kinds to live an endurable life for years, nay, perhaps decades. Mackenzie and his pupil, Lewis, and Warburg are of the opinion that, on the whole, digitalis affects only cardiac insufficiency with congestion, and is useful, above all, in cases in which auricular fibrillation is present. The physician of today knows that in the typical case of cardiac insufficiency, with all its cardinal symptoms, such as dyspnea, a swollen liver, edema, and a rapid, irregular pulse, there is often a prompt response to digitalis, with increased diuresis, reduced pulse frequency, an even, regular pulse, a reduction of the liver swelling, and increasing working capacity. In spite of the enormous progress that physiology has made during the last 30 years, and the employment of physiologic methods in the cardiac clinic, it has not yet been possible to establish with certainty whether digitalis increases the amount of blood the human heart pumps per unit of time, i.e., its minute volume. In 1938, I found that, in cases of congestive heart failure, digitalis instantaneously leads to an increased oxygen consumption by the patient, which probably implies that the blood flow increases, i.e., that the minute volume of the heart increases. Further, I have shown that digitalis may increase the performance capacity, as measured with my function test, in latent cardiac insufficiency, i.e., in cases in which objective signs of heart failure are absent when the patient is examined during rest.

By means of modern electrocardiography we are today able to establish that digitalis can eliminate flutter and fibrillation, the presence of which may be the cause of both an extremely rapid and an irregular action of the heart. Such rapid contractions of the auricle, 300 to 600 times per minute, which are extremely wasteful with respect to the work of the heart, may at times be checked by the administration of digitalis, and be followed by normal sinus rhythm at a rate of 60 to 80 beats per minute. Very frequently, neither flutter nor fibrillation can be eliminated by digitalis, but nevertheless the remedy—and this is extremely usual—blocks the transmission of these waves to the ventricles, so that perhaps only a fraction of the waves are transmitted, and the work of the heart is thereby facilitated.

Innumerable preparations of digitalis have seen the light of day. The original digitalis leaf, in powdered form, still retains its place, however. Of the preparations in more or less pure form, emanating from firms all over the world, "Digalen" is probably one of the best known. In Sweden we have had "Digitotal" for a decade, and, during recent years, "Digiton." Research and industry have proceeded hand in hand on this subject, and the last word has probably not been said as to the effect of the different constituent elements of the digitalis leaf. Commissions have been set up to study these questions, and attention must be drawn in particular to the Dutch Commission, which was entrusted with the task of cooperating with prominent experts, physicians, and pharmacologists in investigating the effects of digitalis. The work of the Commission was published in book form in 1923, and, in the introduction, it is said that if Withering's monograph is compared with what has been written about digitalis during recent years, the volume of the latter is amazing, but unfortunately there is very little new in it which is of undisputed importance in practice and which had not already been given in Withering's classic work.

Thanks to indefatigable efforts, Emil Hultmark, Ph.D., has succeeded in tracing the portrait of Withering by the Swedish artist, F. von Breda, and it now has a place in the National Museum in Stockholm.

Breda painted the portrait in Withering's home, Edgbaston Hall, in 1792. The resemblance is said by his son and one of his friends to have been striking. The position, the expression round the mouth, and the hand which nonchalantly, yet constrainedly, grasps some sprays of digitalis, conform well with the picture Mrs. Schimmelpenninck gives us of Withering. As has been mentioned above, her father and Withering were members of the Lunar Society. She describes Withering as friendly but reserved and uncommunicative; esteemed as he was, he never was among the really popular members of the Society. In the portrait, an unconscious nobility rests on the well-shaped forehead, the long nose, and brushed back, slightly powdered hair. Withering is said to have been very particular about his attire. It is true that at

that time it was the custom always to paint so-called beautiful hands, but one likes to believe that the elegant hand holding the digitalis resembled Withering's own. Finally, with his colors and his brush work, Breda has managed to hand down to us something of the strength and acuteness of intellect which were characteristic of William Withering.

I wish to proffer my warm thanks for their interest and ready cooperation to Dr. Emil Hultmark, and especially to Dr. Erik Waller. Dr. Waller kindly placed at my disposal both his eminent learning and his private library.

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ANGIOCARDIOGRAPHY AND ITS VALUE

Dr. Rodolfo Pérez de los Reyes,* Dr. Agustin Castellanos,† and Dr. Raul Pereiras,‡ Havana, Cuba

ANGIOCARDIOGRAPHY as a method of cardiovascular exploration was presented by two of us (Dr. A. Castellanos and Dr. R. Pereiras, with Dr. A. García) toward the end of 1937, after it had been employed for many months on our cardiac patients. Since that time we have used it systematically in the examination of cardiac patients, and it has become a routine, for it proved to be quite harmless and its diagnostic value surpasses by far that of any other method.

After our work, Steinberg and Robb, of New York, applied the same method to adults with extraordinary success. They performed hundreds of intravenous injections of the opaque substance at high speed without any accident.

Is the word "Angiocardiography" a new medical term? W. A. Newman Dorland, member of the Committee for the Nomenclature and Classification of Diseases of the American Medical Association, has recognized the word "Angiocardiography" as a new scientific term, and included it in the 1941 edition of the American Illustrated Medical Dictionary. *Angiocardiography* means roentgenographic visualization of the heart cavities and large communicating vessels by means of a radiopaque substance. In 1936, several French authors, among whom Ameuille is remembered best, employed the method heralded by Moniz, of Lisbon, of injecting the contrast medium through a catheter which had been introduced as far as the right auricle, and in this way obtained roentgenograms in which the right auricle and ventricle and the trunk of the pulmonary artery were visualized. For this purpose they employed a 120 per cent solution of sodium iodide. However, the difficulties of catheterization of the auricle, as well as the great toxicity of the large amount of iodide, compelled these authors to state that the method could not be employed routinely.

Our first work on angiocardiography was done in 1931, and in 1937 we devised an easy, harmless technique which we have continued to use until the present time. Angiocardiography is a strictly original method, for, previous to the work of Castellanos and Pereiras, no attempt had been made to use peripheral veins for visualizing the human heart cavities and their large communicating blood vessels.

What is the purpose of angiocardiography? It was devised with a view of establishing correct diagnoses of congenital heart disease. *Post-*

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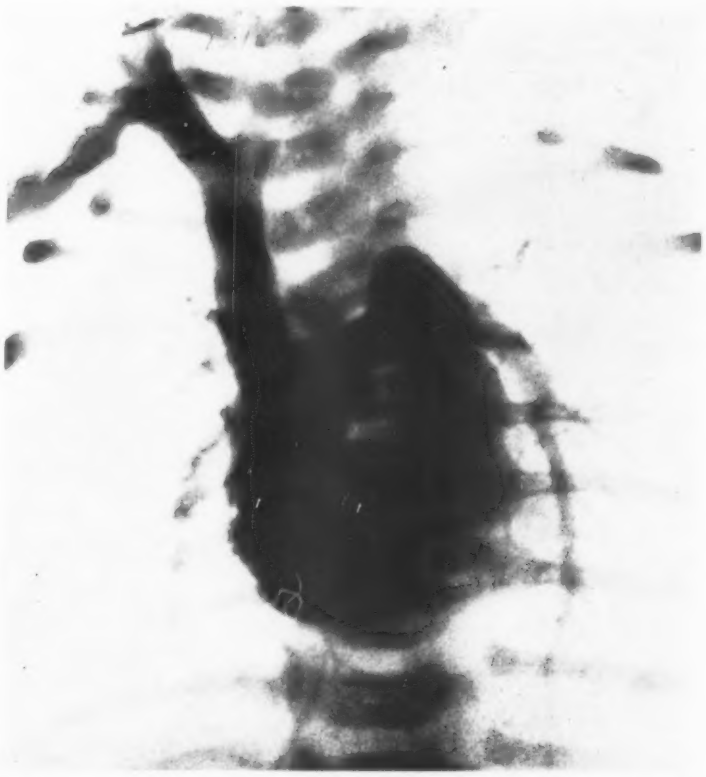

Fig. 1.—Normal angiocardiogram, anteroposterior view; newborn child.

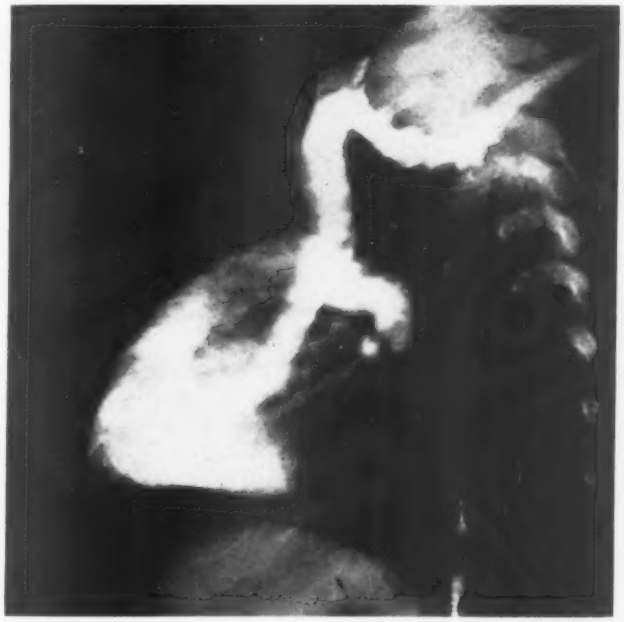

Fig. 2.—Normal angiocardiogram, lateral view; baby, 4 months old.

mortem angiocardiography is performed in cases in which autopsy is refused; it provides distinct images, when carried out with an adequate technique, and its diagnostic value is as great as that of angiocardiography in the living subject. Moreover, angiocardiography furnishes many valuable data in other conditions, such as situs inversus, mediastinal displacement, etc.

How is an angiocardiogram obtained? The technique of the method is very simple, and consists of two main stages:

(1) Introduction of a thin Lindeman trocar in a vein of the elbow, hand, leg, or thigh.

(2) Injection of the radiopaque substance and exposure of the x-ray film at the end of the injection.

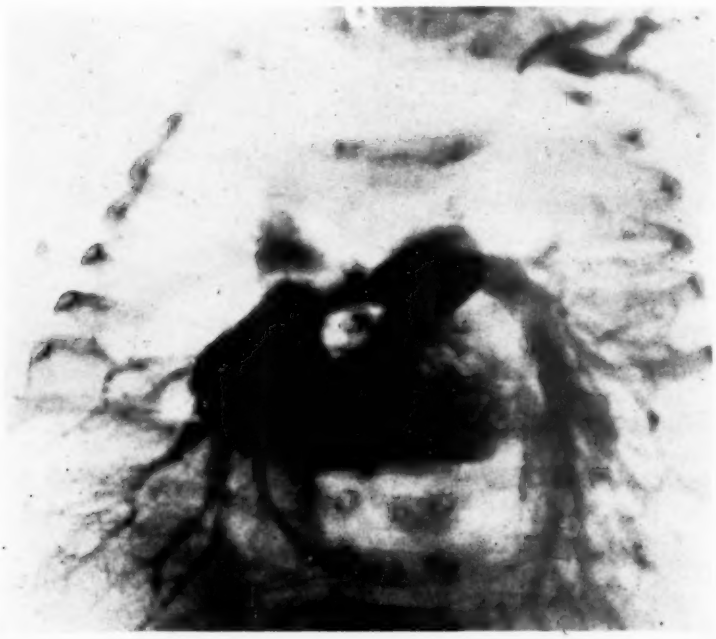

Fig. 3.—Interventricular communication, with slight stenosis of pulmonary artery. Anteroposterior view.

The gauge of the trocar will vary according to the development of the venous system of the patient and his age. The quantity of contrast medium to be injected depends not only on the age and weight of the patient, but also on the presence or absence of cyanosis, because the more pronounced the cyanosis the greater will be the quantity of radiopaque substance required for obtaining proper contrasts. On an average, 8 to 10 c.c. are employed in a newborn child, and 12 to 20 c.c. in an infant. In older children, the quantity will vary between 15 and 30 c.c.

Although sodium iodide should never be used in the living, there are many other substances, such as per-abrodil, uroselectan, hippuran, etc.,

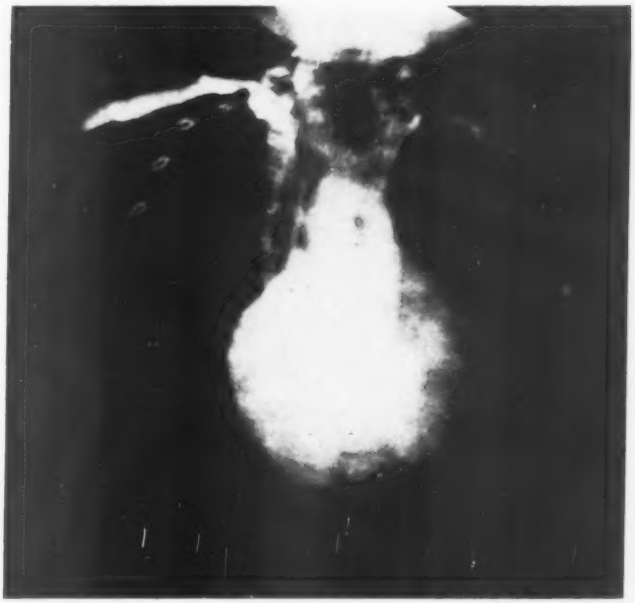

Fig. 4.—Total transposition of the large vessels. Anteroposterior view. The aortic shadow is very dense because the artery is arising from the right ventricle.

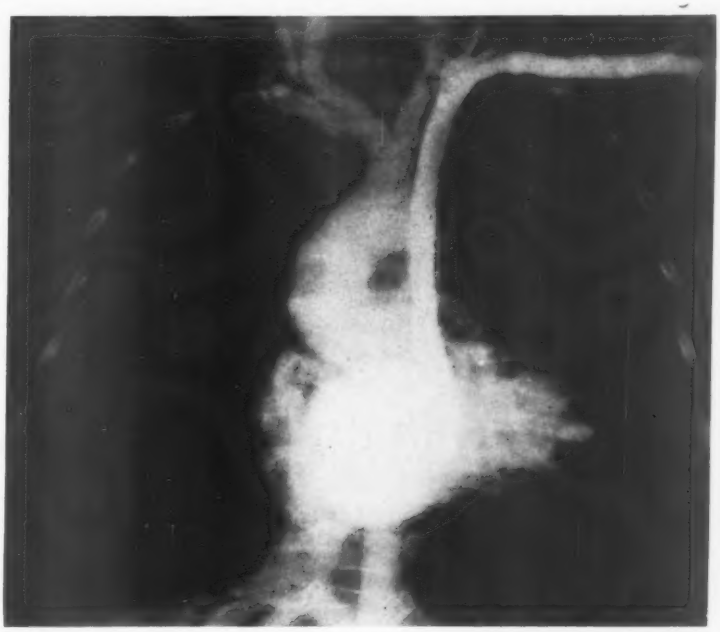

Fig. 5.—Persistence of left superior cava. Left auricle visualized. Interventricular communication. Aorta and its branches visible. Hypoplasia of pulmonary artery. Below the cardiac shadow lie the inferior cava and suprahepatic veins.

which give satisfactory results when employed in concentrations of 35 to 70 per cent. The injection must be carried out within one and one-half to two seconds.

From birth until six months of age we use a 35 per cent solution of the radiopaque substance. From six months until two or three years

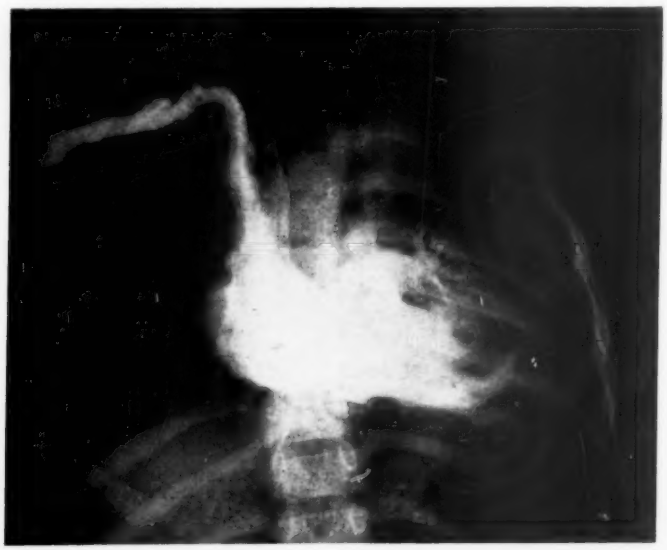

Fig. 6.—Interventricular communication. (Partial agenesia of septum.) Pulmonary stenosis. Anteroposterior view.

Fig. 7.—Tetralogy of Eisenmenger, anteroposterior view. Interventricular communication. Dextroposition of the aorta, which arises above the defect. The pulmonary artery is normal.

of age we may use the same solution in noncyanotic patients, but, in the presence of cyanosis, the best concentration is 50 per cent.

The injection of the radiopaque substance must be completed as rapidly as possible, and the roentgenogram made before the syringe is entirely emptied, i.e., when it still contains two or three cubic centimeters of the solution.

It is possible to obtain anteroposterior and lateral views with a single injection by employing two x-ray tubes and two films.

We employ a special apparatus which permits automatic injection into the vein and exposure of the film at the right moment, without any other manipulation on the part of the operator. It is also advisable to use a special arrangement for maintaining complete immobilization of even the most unruly patient.

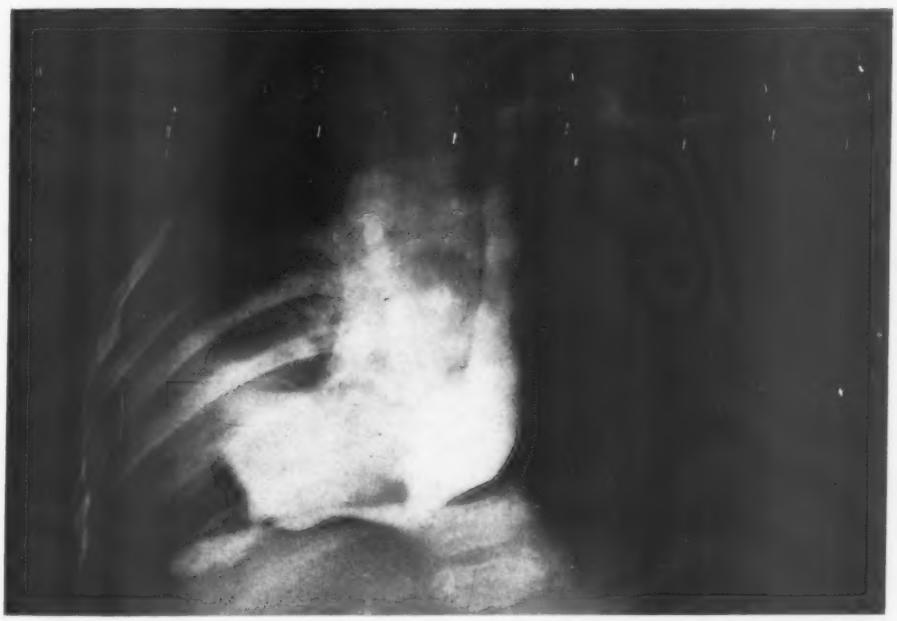

Fig. 8.—Congenital dextrocardia, anteroposterior view. Very large interauricular and interventricular communication.

What is an angiocardiogram? A normal angiocardiogram is easily interpreted, be it an anteroposterior or lateral view. In the anteroposterior view the axillary and subclavian vein, the corresponding brachiocephalic vein stem, the right auricle and ventricle, the stem and branches of the pulmonary artery, and sometimes even the thinnest ramifications of the pulmonary artery become apparent. Usually, the image is U shaped. In the lateral view, the same structures are seen, especially the pulmonary artery as it passes in a semicircle from the infundibulum to its site of bifurcation.

Pathologic angiocardiograms are very interesting, and some amount of experience will permit their correct interpretation. Stenosis of the

pulmonary artery produces a characteristic image which enables one to differentiate the orificial and the infundibular type. It also reveals the extent of the malformation. Patency of the interventricular septum may be diagnosed by indirect signs, such as indentation of the border of the right ventricle, the presence of radiopaque substance within the left ventricle, or sometimes directly by visualization of the communication itself. Transposition of the large vessels, Fallot's tetralogy, and interauricular communications are likewise revealed by characteristic features. In some instances one can also detect patency of the ductus arteriosus by direct or indirect signs. In other cases the method reveals gross malformations of the septum or the presence of a single auricle or ventricle. A single arterial stem produces a typical shadow which indicates common origin of the aorta and pulmonary artery.

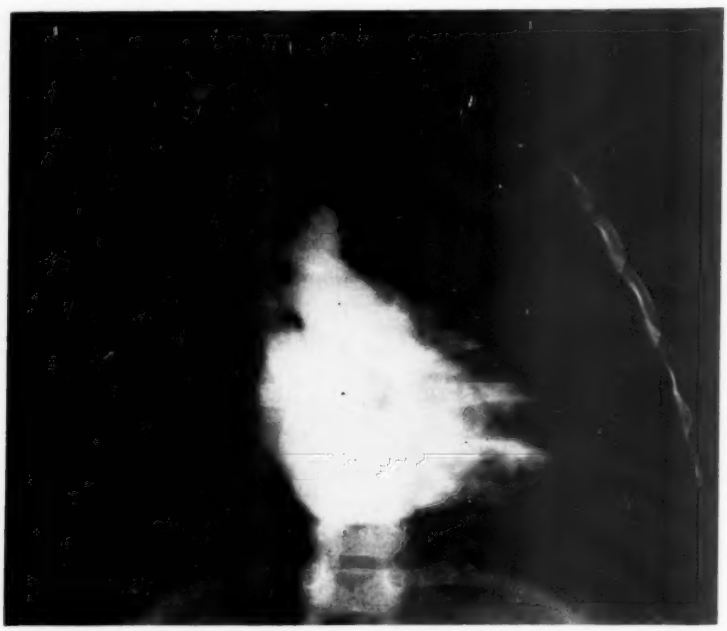

Fig. 9.—Large interventricular communication. The aorta is deviated to right side over the right bronchus (Corvisart type).

Is angiocardiography harmless? The experimental work of Reboul, Racine, Contiades, Ungar, and Naullau proves that the dosage employed by us is quite harmless. This has also been corroborated by the recent work of Robb and Steinberg. We have never seen any serious angiocardiographic accident since we began to employ the method three years ago. Robb and Steinberg have had the same experience in a series of about a hundred injections. We wish to emphasize that we have employed the method in the preagonal and agonal stages of heart disease. We do not refer to cases of heart failure or grave cardiac insufficiency, for almost half of all patients studied by us had reached this stage.

The value of angiocardiography. It is the most accurate method of cardiovascular exploration used at present for the diagnosis of congenital heart disease. It does not furnish indirect evidence, as is the rule with electrocardiography, radiokymography, orthodiagraphy, teleradiography, phonocardiography, and blood gas analysis, but direct anatomic information concerning the chambers of the heart and the great vessels.

When we started our research we made post-mortem angiocardiograms, and then, at autopsy, studied the relations between the images and the deformities. Later, in the course of the last three years, we have continued to perform autopsies on patients on whom we had obtained angiocardiograms during life. This procedure has shown that angiocardiographic diagnoses are surprisingly accurate, for, in every instance, the roentgenogram was characteristic of whatever vascular deformity or abnormality of the septa happened to be present.

Dr. J. M. Martínez Cañas, our eminent cardiologist, remarked in the course of a discussion of our investigations at the Cuban Society of Cardiology that angiocardiography was a method of doing an autopsy on the living.

Dr. Pedro L. Fariñas, in one of his last papers, says that the angiocardiographic method of Castellanos and Pereiras has revolutionized the diagnosis of congenital heart disease.

Other methods derived from angiocardiography. Angiocardiography has given rise to other methods, such as visualization of the inferior and superior venae cavae, and, above all, to retrograde aortography, or aortography by countercurrent. This is a special method for diagnosis of patency of the ductus arteriosus, and consists mainly in introducing a thin trocar into the left brachial artery, maintaining an Esmarch ligature below or behind this site, and injecting a radiopaque substance. The contrast medium passes in a retrograde, or centripetal, direction into the left subclavian artery and the arch of the aorta, and the latter stands out in great contrast. If there is patency of the ductus arteriosus, some of the contrast medium appears in the pulmonary artery after having passed through the ductus arteriosus itself.

CONCLUSIONS

1. We were the first to demonstrate that the heart cavities and great vessels can be visualized by injecting a radiopaque substance into a peripheral vessel.

2. This procedure, which we call angiocardiography, is the most accurate method for diagnosing cardiac abnormalities.

3. The technique is easy, and it can be done wherever there is roentgenographic equipment.

4. The interpretation of normal and pathologic angiocardiograms does not present any difficulties.

5. In view of its rapidity and accuracy, angiocardiography is indispensable in the study of heart disease.

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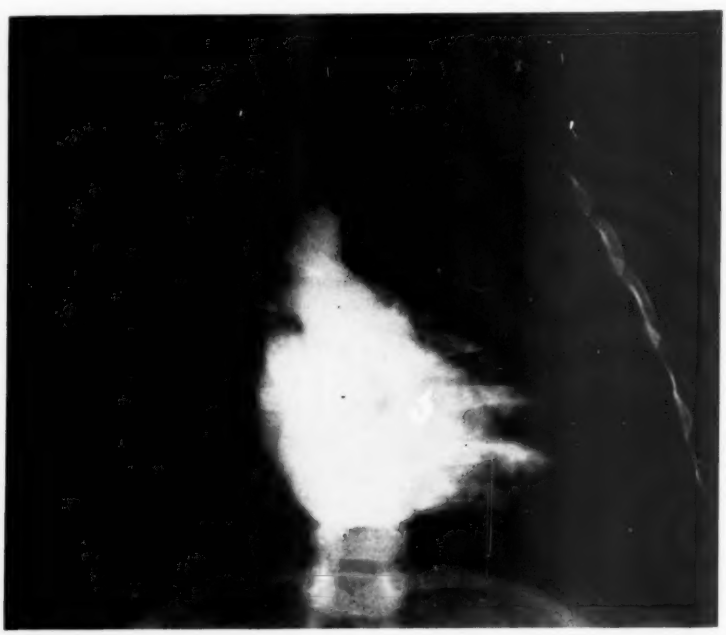

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THE SEROLOGIC REACTION IN CARDIOVASCULAR SYPHILIS

WALTER BECKH, M.D., SAN FRANCISCO, CALIF.

WHENEVER the clinician is confronted, in differential diagnosis, with cardiovascular syphilis, the question immediately arises: How often is the serologic reaction positive in syphilitic heart disease? That the answer to this query is usually not very clear is a reflection of the indefinite state of affairs which exists in regard to the serologic situation in cardiovascular syphilis. The study presented here was undertaken to clarify this point. In addition, an attempt was made to ascertain what other criteria may be of aid, beyond those now known, in making a correct clinical diagnosis of cardiovascular syphilis.

Since the Wassermann reaction was first described, over thirty-five years ago,[1] its aid in the diagnosis of syphilitic heart disease has been invoked. However, a glance at the literature (Table I) regarding the incidence of positive serologic tests shows a wide discrepancy of figures. The reasons for this are several. First, in numerous reports the percentage of seropositivity has been arrived at by ascertaining its incidence in cases in which the clinical diagnosis was cardiovascular syphilis. Although the clinical diagnosis of aneurysm and aortic insufficiency can be made in many cases with a fair degree of certainty, this becomes an entirely different matter in cases of uncomplicated aortitis. In a paper published in 1932, Moore, Danglade, and Reisinger[4] listed certain criteria for the clinical diagnosis of aortitis, but further review of their diagnostic points did not substantiate the conclusions they had reached.[14, 19, 20] The diagnostic criteria set up by Maynard[21] may be an answer to this problem, but so far not enough data have been accumulated to be convincing. It may therefore be asserted that at present the diagnosis of uncomplicated aortitis is generally considered impossible.

Second, another source of error in accepting the figures in the literature lies in the fact that the sensitivity of the Wassermann reaction has undergone frequent and marked changes. Increasingly sensitive tests have been added to our serologic armamentarium. We find that practically all studies have included a large percentage of cases dating back to an era in which the Wassermann test, by modern standards, was quite insensitive. Such reports can therefore be only misleading when the incidence of seropositivity in cardiovascular syphilis at the present time is considered.

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Presented at the meeting of the California Heart Association, Del Monte, May 2, 1942.

Received for publication June 1, 1942.

TABLE I

THE WASSERMANN REACTION IN CARDIOVASCULAR SYPHILIS (HISTORICAL REVIEW)

SEROLOGIC TEST	AORTITIS		AORTIC INSUFF.		ANEURYSM		EXACT DIAGNOSIS OR HISTORY OF TREATMENT NOT SPECIFIED	YEAR	DIAGNOSIS	AUTHOR
	TREATED	NOT TREATED	TREATED	NOT TREATED	TREATED	NOT TREATED				
Not specified							57.5%	Up to 1923	Clinical	Stokes and Anderson[2]
Kahn							81.8%	1929	Clinical	Miller[3]
Kline							84.8%	1929	Clinical	
Not specified	75%							1919-1930	Pathologic.	Moore et al.[4]
Not specified	65%		68%		83%			Up to 1930	Pathologic.	Willius[5]
Not specified							76%	1912-1930	Pathologic.	Reid[6]
Wassermann (water bath)							85%	1920-1930	Clinical	
Wassermann (icebox)							95%	1920-1930	Clinical	Eagle[7]
Wassermann (i.b.) or Eagle							95-100%	1920-1930	Clinical	

Wassermann			93%		93%			Up to 1931	Clinical	Carter and Baker[8]
Wassermann			"Nearly 93%"		"Nearly 93%"			Up to 1931	Pathologic.	Carter and Baker[9]
Not specified							90%	Up to 1934	Pathologic.	Scott[10]
Not specified	52%	83%						Up to 1936	Clinical	Cole and Usilton[11]
Not specified			85%					Ditto	Clinical	Cole and Usilton[12]
Not specified					45%	90%		Ditto	Clinical	Cole and Usilton[13]
Wassermann, Hinton, or both	90%							Up to 1937	Pathologic.	White and Wise[14]
Kahn	About the same percentage in all three categories						92%	Up to 1938	Clinical	Wile and Snow[15]
Wassermann							Less than 85%	Up to 1940	?	Gager[16]
Wassermann or Kahn	70%		95%		95%			1940	Pathologic.	Gouley and Anderson[17]
Wassermann				98%				1936-1940	Clinical	McDermott et al.[18]

Third, the question of treatment previous to study is one frequently not mentioned, a point which admittedly may be of great significance.

And, fourth, a history of a previously positive serologic reaction or a history of previous antisyphilitic treatment might be of great aid in making a diagnosis.

This report presents a review of 100 consecutive cases of cardiovascular syphilis, *diagnosed at autopsy*, in which the histories provided adequate data for study. These cases were for the most part from the Stanford Medical Service of the San Francisco Hospital, although six had been patients at the Stanford Medical Service at Laguna Honda Hospital, the chronic disease division of the San Francisco county institutions. These patients came to necropsy between March 1, 1933, when the laboratories of the San Francisco Department of Public Health added the Kahn test to the already routine Wassermann reaction, and January 12, 1942. The serologic technique was altered at no time during this period. In the evaluation of serologic positivity there have been included in the seropositive group all those cases in which there was a positive Wassermann or Kahn, or both.

In a survey of the data, we find, in contrasting the varieties of lesions, that there was no essential difference in the distribution of aortitis, aortic insufficiency, and aneurysm between the seropositive and the seronegative group.

In studying the effect of previous antisyphilitic treatment on the Wassermann and Kahn reactions (Table II), the figures suggest that therapy is only of moderate importance.

TABLE II

EFFECT OF TREATMENT

ON SEROLOGIC REACTION IN CARDIOVASCULAR SYPHILIS

TREATMENT	SEROPOSITIVE GROUP 87 CASES	SERONEGATIVE GROUP 13 CASES
"Much"	10%	31%
"Little" or none	73%	62%
Uncertain or unknown	17%	7%

"Much" treatment—twenty or more injections of a trivalent arsenical and a corresponding amount of bismuth.
"Little" treatment—less than this amount.

The average age in the seronegative group was 69, as against 55 in the seropositive, which is perhaps an indication of spontaneous arrest.

In view of the small number of cases in the seronegative group, the data thus far can be taken merely to indicate a trend. Because we think that the clinical diagnosis of syphilitic aortitis in the uncomplicated form is still impossible, the figures in Table III concerning the incidence of positive reactions in uncomplicated aortitis are, for the present at least, merely of academic interest. Despite the high incidence of positive Wassermanns (86 per cent), the clinical diagnosis of aortitis

TABLE III

THE INCIDENCE OF A POSITIVE SEROLOGIC REACTION IN CARDIOVASCULAR SYPHILIS

PATHOLOGIC DIAGNOSIS	NO. OF CASES	SEROPOSITIVE	SEROPOSITIVE OR HISTORY OF POSITIVE SEROLOGIC REACTIONS OR HISTORY OF TREATMENT
Aneurysm or aortic insufficiency or both	49	43 (88%)	47 (96%)
Uncomplicated aortitis	51	44 (86%)	46 (90%)

was not made in a single instance. However, the figures may be of some importance because they are at variance with the statement of Gouley and Anderson,[17] who said, in 1940, that "it is now well known that the Wassermann and Kahn tests are negative in about 30 per cent of the patients who at necropsy exhibit syphilitic aortitis."

In aortic insufficiency and aneurysm, the diagnosis is made with considerable certainty in many instances, but at times the clinical problem is very vexing. Therefore, our data are of particular interest.

In Table III the clinically diagnosable group of cases, namely, those with aneurysm and aortic insufficiency, has been separated from those of uncomplicated aortitis. Of the 49 cases in this former group, in 43, or 88 per cent, there was a positive Wassermann or Kahn, or both, on the first examination. However, when to this figure we add those seronegative patients who gave a history of a previously positive test or of previous antisyphilitic treatment, the percentage total increases to 96 per cent. This is important because a history of previous antisyphilitic treatment or a previously positive serologic reaction is information that is readily obtainable from the patient and is not subject to individual misinterpretation such as a "history of syphilis" which may in reality represent lymphopathia venereum or a mere herpes genitalis.

SUMMARY AND CONCLUSIONS

A study of 100 cases of cardiovascular syphilis, *diagnosed at autopsy*, in which the serologic reactions had been done by a modern technique, is presented. Of 49 cases of aortic insufficiency or aneurysm or both, in 43, or 88 per cent, there was a positive Wassermann or Kahn or both on first examination. Of 51 patients with uncomplicated aortitis, 86 per cent had a positive serologic reaction. In none of the cases of aortitis was the diagnosis made clinically.

Of the 49 patients with clinically diagnosable cardiovascular syphilis, i.e., aortic insufficiency or aneurysm or both, 96 per cent had either a positive Wassermann or Kahn or both, or a history of a positive Wassermann in the past, or, lastly, a history of previous antisyphilitic treatment.

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AN APPARENT CAUSAL MECHANISM OF PRIMARY THROMBOSIS OF THE AXILLARY AND SUBCLAVIAN VEINS

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THROMBOSIS of the axillary and subclavian veins may be caused by infection of regions adjacent to, or drained by, these veins, by invasion or compression by neoplastic tissue, by direct external trauma, or by some unknown mechanism related to forceful or sustained motion of the shoulder girdle or arm on the affected side. The diagnostic term, primary or effort thrombosis, is applied to the cases that fall into the last group, and it is with this group that this paper is solely concerned.

Although the literature on primary thrombosis of the axillary and subclavian veins is increasing, and excellent reviews on this subject have been published by Matas,[1] Hammann,[2] and others, the condition is not common. In most instances only single cases are reported. The eight case histories presented by Gould and Patey[3] constitute the largest series investigated by any workers. There has been a singular paucity of reports in the American literature. In this paper, five case histories from the Medical Division of the University of California Hospital are presented, and an explanation of the causative mechanisms is offered.

Paget,[4] in 1875, described spontaneous thrombosis of the veins of the upper extremity under the classification of "gouty phlebitis," and cited similar cases reported by Mackenzie, in 1862, and Humphry, in 1869, but the first adequate clinical recognition of the condition is generally credited to von Schroetter,[5] in 1884. Considerable time elapsed between this report and the general awakening of interest in the condition, beginning in 1911, in Germany, Great Britain, France, and Switzerland.[6-14]

The condition usually occurs in healthy young males who are engaged in vigorous muscular activity, but it may occur at any age from childhood onward,[10] and in either sex. As would be expected, the right arm, because of its more general use, is more frequently affected than the left. Paggi[15] found that the ratio of involvement of the right arm to the left was 2.5 to 1. The onset may be heralded by pain in the shoulder or arm, or it may be painless. Turgidity and edema may develop in the arm immediately after the suspected causative effort, or hours or days may elapse between the apparent cause and the signs of a thrombosed vein. The skin is usually cyanotic; the superficial veins of the arm and the collateral veins of the shoulder and upper part of the chest

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are often distended within a few hours after the onset of edema. The venous pressure has been found by Veal[16] to be elevated; both he and Cottalorda[17] reported elevated systolic and diastolic brachial arterial blood pressure on the affected side. A palpable, tender cord is often felt in the region of the brachial and axillary veins shortly after the onset of signs and symptoms. Local signs of inflammation rarely are found. With rest of the extremity, the edema and stiffness may subside in as short a time as five days, but they usually last from two to eight weeks, and often recur with active use of the arm for five or six months and occasionally for as long as six years.[18] Operative removal of the thrombus has been advocated in order to facilitate more rapid recovery.[1, 15, 19]

The types of precipitating effort vary considerably, and may be classified as follows:

Type 1. No unusual effort or motion.[3, 16, 20, 21, 22]

Type 2. Lifting of heavy weights.[1, 23-26]

Type 3. Long sustained and moderately vigorous activity involving the arm or arms and shoulder girdle:
- a. Holding a high-spirited riding horse with the left hand (left arm involved).[7]
- b. Holding back a team of driving horses.[27]
- c. Rowing a boat.[22]
- d. A police officer struggling to hold an arrested person.[28]
- e. A soldier loading and unloading a piece of field artillery.[29]
- f. Long stirring of heavy pudding mixture.[30]
- g. Scrubbing clothes for a long time.[16]
- h. Carpentry work, presumably sawing and planing.[26]
- i. Throwing a ball or a rock.[10, 31]
- j. Playing a strenuous game of golf (left arm involved).[3]
- k. Patient pushing himself up in bed.[33]

Type 4. Minimal effort involving frequent or sustained elevation of the arm or arms over the head:
- a. Screwing in curtain rods high over head.[3]
- b. Placing jars on a high shelf.[3]
- c. Cleaning a ceiling.[3]
- d. Hanging meats on high hooks.[10]
- e. Exercises of elevating arms over head.[32]
- f. Sleeping with arms extended upward under the head.[16]

Many cases in which no precipitating effort was reported may have been examples of Type 4. A careful history perhaps would have revealed a period of unusual elevation of the arms.

Five cases of primary thrombosis of the axillary and subclavian veins are presented.

CASE 1.—(Figs. 1 and 2). D. R. J., 30 years of age, was a broad, moderately deep-chested, right-handed, healthy appearing man whose natural posture was such that the shoulders were held back and the clavicles were directed upward and posteriorly. He entered the University of California Hospital November 6, 1940. One week earlier, after pitching a baseball, he had noted a pulling pain in the right axilla and the deltoid region, followed by mild soreness which disappeared completely within twelve hours. On the next day the entire right arm felt numb for five minutes after

he had pitched a baseball. He noted tenderness on pressure in the right axilla for a week, but pain did not recur until the day he entered the hospital. About four hours prior to entry, after playing a set of tennis, he noted swelling of the right forearm. After he had played two more sets he noted that his entire right arm was

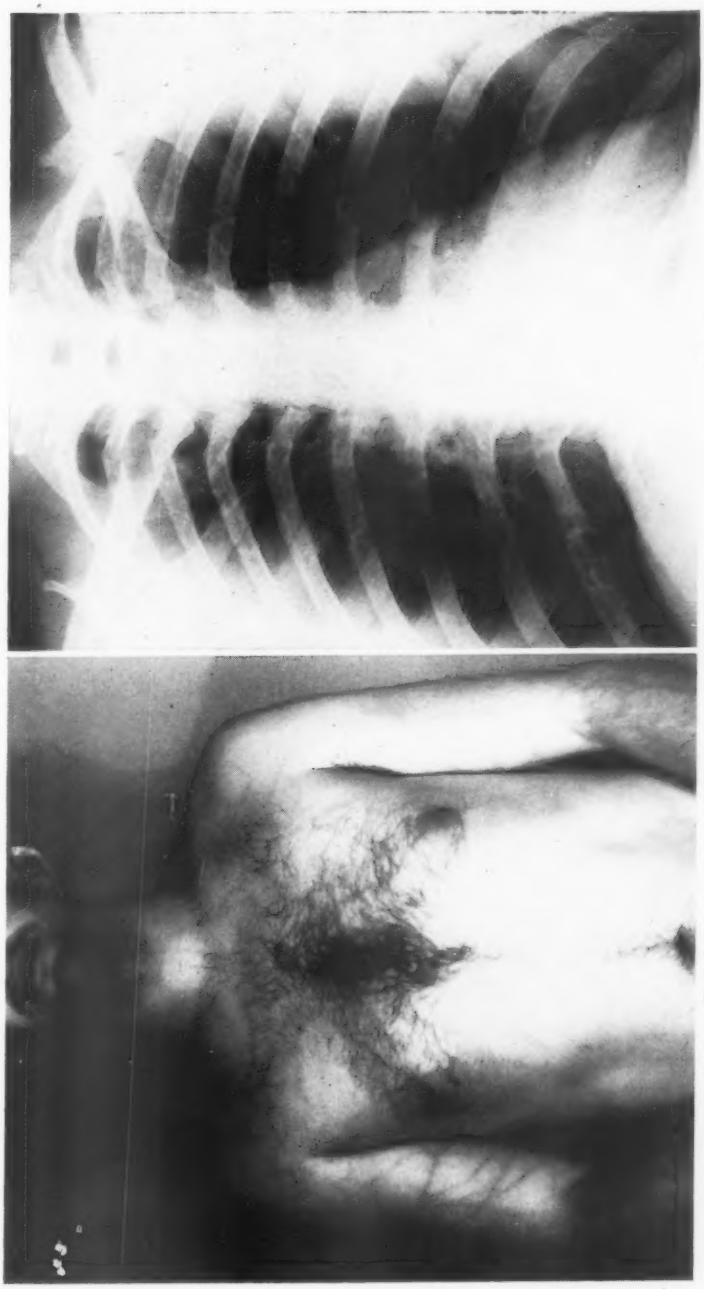

Fig. 1.

Fig. 2.

Fig. 1.—Infrared photograph of patient in Case 1. Illustrates the swelling of the affected right arm and the distended superficial veins of the arm, shoulder, and pectoral region. The broad chest and posteriorly directed clavicles are evident. (Reproduced from Medico-Surgical Tributes to Harold Brunn.)

Fig. 2.—Roentgenogram of the upper chest and shoulder in Case 1. The high, widely sweeping first ribs and the posteriorly directed clavicles are illustrated. (Reproduced from Medico-Surgical Tributes to Harold Brunn.)

swollen and cyanotic, and he felt an aching pain and numbness throughout the arm from the shoulder to the hand. The pain disappeared in half an hour.

Physical examination revealed that the posterior curvature of the right clavicle was greater than that of the left. The entire right arm, to the shoulder, was swollen, cyanotic, and moderately indurated. The superficial veins of the hand and arm, as well as the superficial collateral veins over the shoulder and upper right pectoral region, were dilated. A tender, firm cord extended from the region of the brachial vein into the right axilla. At time of entry the blood pressure was 135/75 in the left, and 140/70 in the right, arm. After complete rest of the right arm for six days, the blood pressure was 124/60 in the right, and 134/70 in the left arm, and the swelling and cyanosis had subsided. At time of entry the rectal temperature was 38.4° C., and the leucocyte count was 12,000; both returned to normal within six days. At time of entry, the venous pressure in the left arm was normal; the veins in the hand collapsed at about the level of the third rib when the patient was in the erect position. The venous pressure in the right arm was elevated; the veins in the hand collapsed 30 cm. above the level of the third rib. The veins over the right shoulder and the pectoral region had become very prominent and showed appreciable upward and mediad blood flow. One week after discharge the venous pressure in the right arm fell to 15 cm. of physiologic salt solution.

The patient was discharged after one week of hospital care. He was examined at intervals during the succeeding six months. Slight swelling in the arm continued for about three months, and thereafter was noted only after activity. The tender cord in the region of the brachial and axillary veins had disappeared.

This case may be classified as Type 3. The physical work involved in throwing the baseball was vigorous and unusual. The striking feature in this case was the long delay between the onset of the pain which probably represented the initial trauma and the occurrence of the thrombosis as a sequel to the secondary trauma of the tennis game. This patient had increased venous pressure and arterial blood pressure in the affected extremity. His partial clinical recovery was prompt.

CASE 2.—(Figs. 3 and 4). S. P. M., a woman, 62 years of age, had had chronic paranasal sinusitis, emphysema, and bronchiectasis, the latter chiefly in the left lower lobe, for at least six years prior to observation in the Out-Patient Department of the University of California Hospital on December 31, 1935. A left-sided phrenicectomy had been done for relief of the last mentioned condition three years earlier. The patient had marked kyphosis, arthritis of the thoracic spine, and anterior protuberance of the upper portion of the sternum. The clavicles were directed upward and posteriorly in her natural erect posture. Two weeks previously, after more than ordinary housework, cyanosis and swelling of the entire left arm and hand, without pain, had set in; this condition had continued unaltered to the time of entry into the hospital.

The left arm and hand were of a mottled, bluish color, and the superficial veins in the extremity and over the shoulder and left pectoral region were distended. No thrombotic vein was palpated, but there was tenderness in the axilla. The blood pressure was the same in both arms, namely, 150/80. After resting the extremity for one week, the swelling and cyanosis disappeared. A year later there was no apparent difference in the two arms, although the left arm ached occasionally on motion.

This case may be classified as Type 1 or Type 3.

CASE 3.—E. M., 37 years of age, was a slender, well-developed man with a somewhat broad and deep upper chest; his clavicles were directed slightly upward and posteriorly in his normal posture. He was a dishwasher in a restaurant, and constantly used the left hand more than the right. Three months, and again one and one-half weeks, prior to his entry at the University of California Hospital on December 5, 1934, he had had attacks of pleurisy on the left and right sides successively,

from which he had recovered completely. No active tuberculosis had been found. One week prior to entry, while lifting the cover of the dishwasher with both hands after washing dishes, he noticed that the entire left arm was purplish in color and felt tense, and that the superficial veins were distended. These changes were less

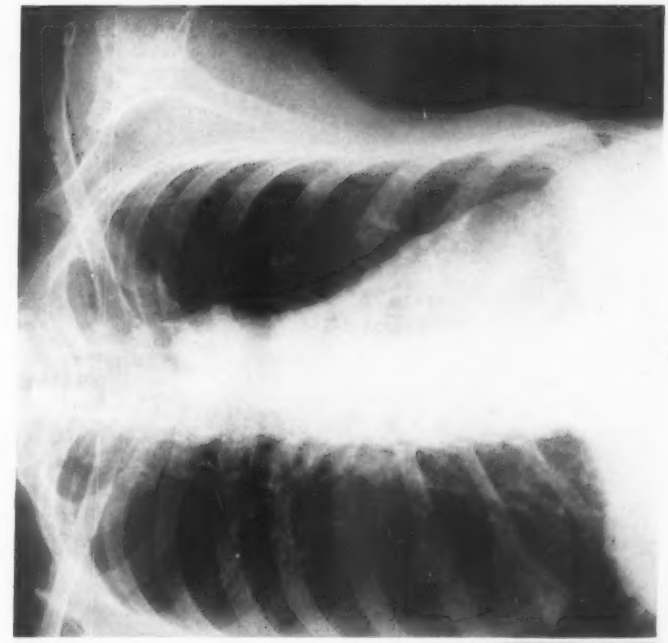

Fig. 4.

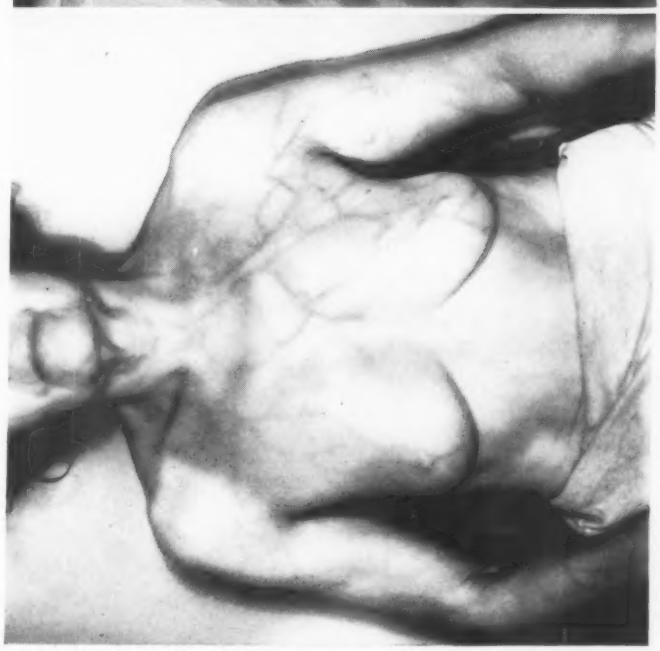

Fig. 3.

Fig. 3.—Infrared photograph of patient in Case 2, illustrating the deep upper chest with posteriorly directed clavicles and the distended veins of the left arm, shoulder, and pectoral region. (Reproduced from Medico-Surgical Tributes to Harold Brunn.)

Fig. 4.—Roentgenogram of the upper chest and shoulder in Case 2. The high, flattened position of the upper ribs and the posteriorly directed clavicles may be observed. (Reproduced from Medico-Surgical Tributes to Harold Brunn.)

marked when he was in a reclining position or when he elevated the arm. He continued work and the arm became increasingly swollen and cyanotic. At the time of his hospitalization the engorged veins extended from the extremity over the shoulder to the margin of the left sternomastoid muscle and over the upper pectoral region to the sternal border. The left infraclavicular and scapular regions were also slightly indurated. No thrombosed veins were felt in the left arm or axilla. The blood pressure was not recorded. There was only slight improvement with rest during the sixteen days of hospitalization. The patient was not followed thereafter.

This case may be classified as Type 2, for the left arm and shoulder were used vigorously in dishwashing.

CASE 4.—M. M., a housewife, 48 years of age, entered the University of California Hospital July 7, 1919, with complaints referable to generalized arthritis and pes planus. She was deep-chested. Four years prior to admission, after no unusual effort other than routine housework, she had observed swelling and cyanosis of the right hand and forearm which had extended rapidly to the entire right arm and shoulder. A tender lump had been noted in the right axilla. A diagnosis of a thrombosed vein in the axilla had been made. The swelling had receded gradually over a period of four months and had not recurred. She had had no pain. At the time of her hospital entry in 1919, the right arm was slightly larger than the left and the superficial veins were more distended, not only over the arm but also over the upper right anterior portion of the chest. The blood pressure was not recorded.

This lesion may be classified as Type 1. No obvious traumatic activity occurred. The persistent recurrence for a period of four years of the signs and symptoms of thrombosis after work involving the right arm was an interesting feature of this case.

CASE 5.—R. P., a carpenter, 22 years of age, a broad, deep-chested man with good muscular development, entered the University of California Hospital March 14, 1916, after intense physical activity (sawing, planing, and lifting wood). On March 12, he noted swelling of the entire right arm from the hand to the shoulder. When he resumed work on March 13, the arm became blue and painful and the superficial veins became increasingly distended. Upon pressure over the axilla, pain radiated down the medial surface of the arm.

Examination revealed that the right arm was mottled, reddish-blue in color, swollen and indurated, and the superficial veins and venules in arm, axilla, shoulder, and pectoral region were distended. A tender cord was palpated in the region of the brachial and axillary veins. Six days later the swelling had subsided, and only a trace of the induration was noted on discharge ten days after admission.

This case, precipitated by vigorous use of the right arm in carpentry, may be classified as Type 3.

The hypotheses concerning the pathogenesis of this condition may be summarized as follows:

1. Von Schroetter[5] stated that trauma of the wall of the vessel was caused by stretching the subclavian and axillary veins and by compression, but he did not give a precise definition of the forces involved.

2. Willan[22] believed that the compressing force was between the medial border of the pectoralis minor muscle and the first rib, and that stretching of the vein occurred.

3. Gould and Patey[3] believed that the pressure of the subclavius muscle on the vein lying on the first rib was the most important traumatic agent. Others, including Aschoff,[6] Löhr,[34] and later investigators tenta-

tively assumed that the subclavius muscle or the clavicle and the first rib were the important compressing agents.

4. Cadenat[35] and Lahaussois[36] presented the theory that distention of the subclavian vein from increased respiratory effort preceded the traumatic compression and contributed to it. This conception was accepted by Lowenstein,[37] Veal and McFetridge,[38] and others.

5. Cottalorda,[17] Löhr,[34] and, more recently, Hammann[2] suggested that primary or secondary spasm of the vein was induced by the trauma and that thrombosis was not necessary for venous obstruction. Occasional operations which failed to reveal a thrombus in the vein confirmed this hypothesis.[39]

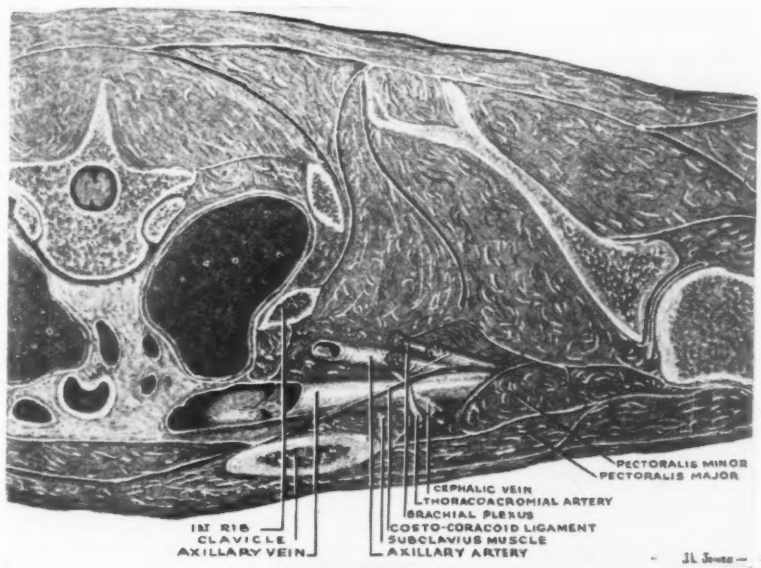

Fig. 5.—Anatomic relationships of the axillary vein, illustrating the costocoracoid ligament which crosses that vessel. (Reproduced from Lowenstein.[37])

6. Lowenstein[37] demonstrated the anatomic relationships of the costocoracoid ligament and presented the hypothesis that compression of the axillary vein was produced by that ligament at a point 35 to 45 mm. distal to the crossing by the vein of the highest point on the first rib (Fig. 5).

7. Veal and McFetridge[38] stated that the compression of the vein which is responsible for the thrombosis occurred in the axilla between the abducted head of the humerus and the subclavius muscle. They demonstrated this hypothesis by diodrast visualization of the veins (Figs. 6 and 7).

8. Lastly, Benda,[40] Moure and Martin,[39] and others believed that a hematoma in the axillary region was often responsible for the compression of the vein.

In 1940, Sampson, Saunders, and Capp[41] presented the hypothesis that partial compression of the subclavian vein by the clavicle or subclavius muscle and the first rib is not an uncommon occurrence, and is responsible for the distention of the superficial veins of the anterior shoulder and pectoral region that is frequently seen. They stated that persons with high, horizontally curving first ribs and upwardly and backwardly directed clavicles tend to show this clinical picture because of compression of the subclavian vein in the first third of its course (Fig. 8). Collateral circulation, which results from the obstruction of the main

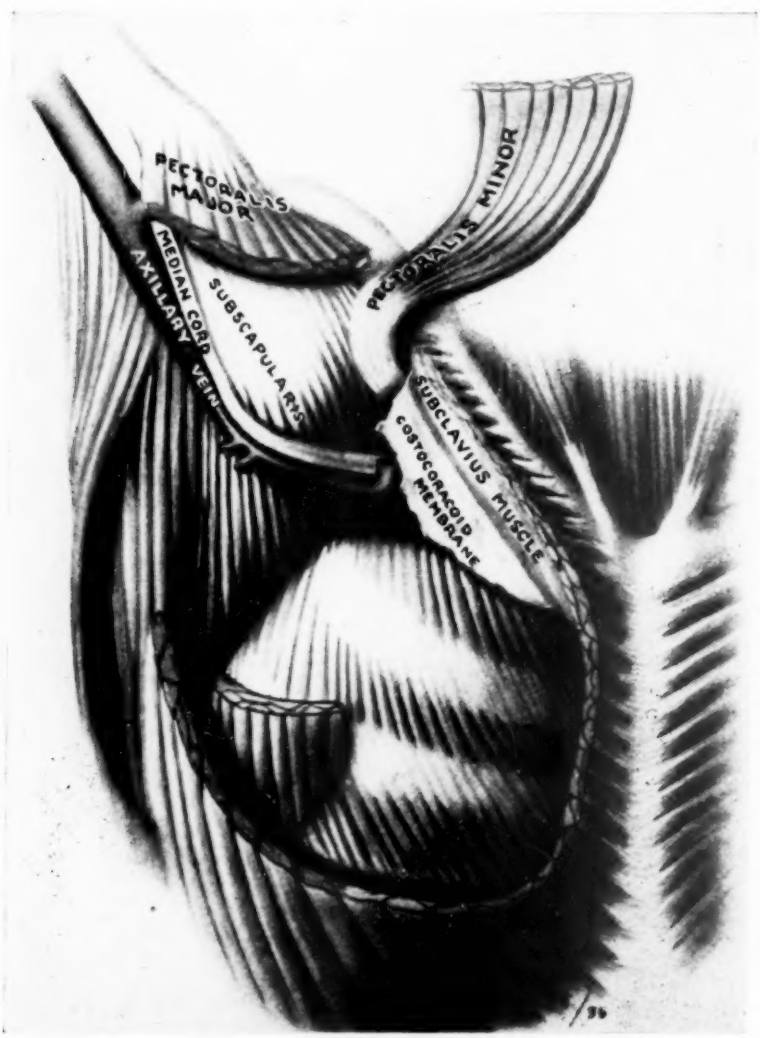

Fig. 6.—Drawing illustrating anatomic relations of parts of the axillary region when the arm is in a position of hyperabduction and external rotation. Note the constriction of the axillary vein against the subscapularis muscle and the stretching of the vein just proximal to the point of constriction. (Reproduced from Veal and McFetridge.[36])

deep channels, increases the pressure in, and the size of, the superficial veins. Persons who tend to have these prominent veins usually have broad chests and good postures, with shoulders naturally held back. Cases were presented to demonstrate that obstruction of the subclavian vein is increased by a voluntary backward thrust of the shoulder girdle without elevation or abduction of the arms (Fig. 9). Thus, those efforts or postures that produce backward and upward (posterior and cephalad) motion of the clavicles tend to obstruct the blood flow in the subclavian vein even if the force of the motion is small and is unassociated with abduction of the arms. Consequently, spontaneous thrombosis of the sub-

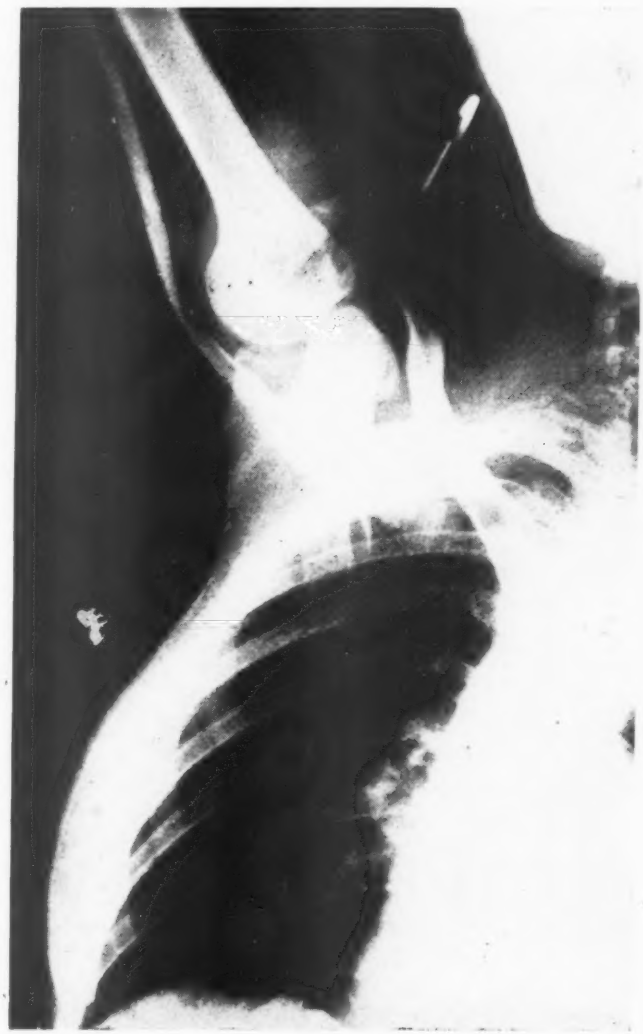

Fig. 7.—Roentgenogram showing point of constriction of the axillary vein below the head of the humerus against the subscapularis muscle in a position of hyperabduction and external rotation. (Reproduced from Veal and McFetridge.[38])

clavian vein may occur as a result of the efforts classified as Types 3 and 4, such as holding the arms over the head to clean a ceiling.

Many investigators have stated previously that the zone of compression of the subclavian vein may be between the clavicle and the first rib, but they have not specifically defined the site or the agencies responsible for the compression. However, Lowenstein[37] and Veal and McFetridge[38] located the compressed segment of the vein lateral to the zone designated by Sampson, Saunders, and Capp.[41] In Fig. 7, from Veal and McFetridge, the radiopaque material does not reveal the subclavian vein proximal to the axilla. Although a compression of the vein in the axilla is demonstrated, a more proximal zone of compression may also have been present without being shown in the illustration.

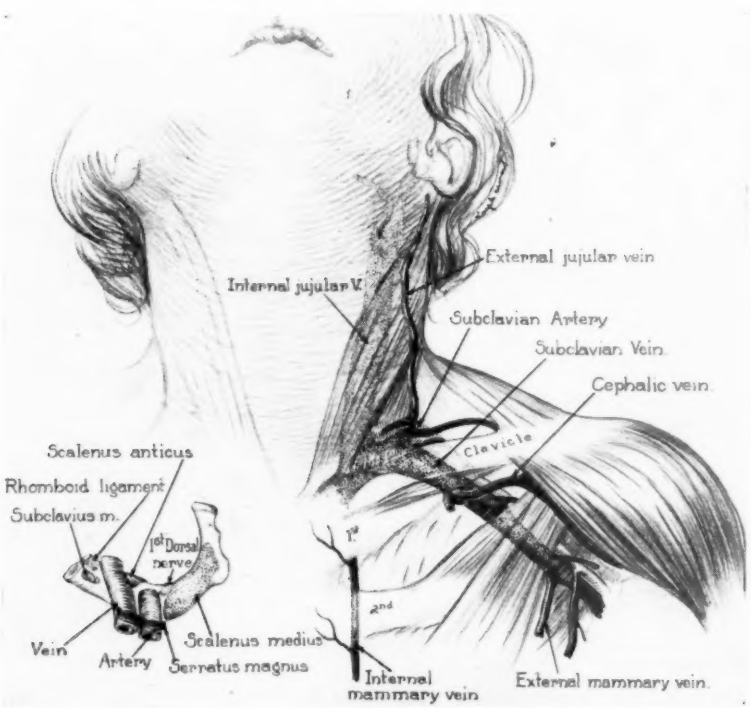

Fig. 8.—Anatomic relationships of the subclavian vein, illustrating its crossing the first rib under the subclavius muscle and clavicle in a narrow triangular space medial to the scalenus anticus muscle. Elevation of the clavicle tends to obliterate this space. (Reproduced from Sampson, Saunders, and Capp.[41])

The mechanism and the zone of compression are well illustrated in a case of Robb and Steinberg.[42] During a diodrast injection for visualization of the heart, the patient's arm was extended over his head. The radiopaque blood was held in the vein distal to the point of crossing, and, after nine seconds, began to flow partially past an obstruction at that point. Roentgenograms taken prior to the time of release of the obstruction confirmed this observation, and another, taken shortly after

the partial return of flow through the subclavian vein, clearly showed that the area of compression was immediately proximal to the crossing of the first rib by the vein (Fig. 10). The patient had an acute thrombosis of the subclavian and axillary veins as a sequel to this incident. This case illustrates a double cause for the local thrombophlebitis, namely, compression which slowed the blood flow, and an irritant, the diodrast. A similar case was that of a girl, thirteen years of age, on whom diodrast

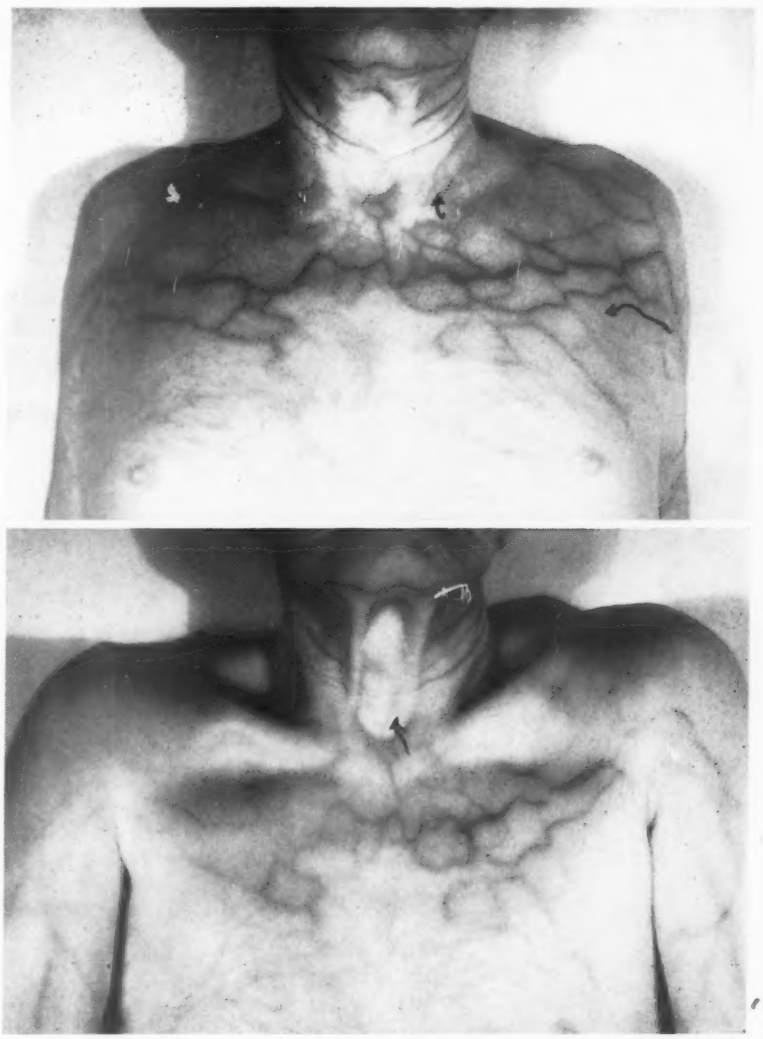

Fig. 9.—Development of prominent collateral veins in a case of chronic compression of the subclavian veins. The patient had a broad, deep chest and "good" posture with posteriorly directed clavicles.

A represents the increased distention of the superficial chest veins when the shoulders are held backward; *B* shows collapse of these veins when the shoulders are held forward. These changes occur with change of position of the shoulder girdle without abduction or elevation of the arms. (Reproduced from Sampson, Saunders and Capp.[41])

visualization studies were made for diagnosis of a congenital heart lesion. No apparent defects were noted in the peripheral arteries or veins. A roentgenogram taken approximately eight seconds after the injection of diodrast into the median basilic vein, with the arm extended over the head, showed that part of the radiopaque blood had flowed into the superior vena cava, but much of it was held in the subclavian vein distal to the point of apparent obstruction which was immediately proximal to the crossing of the first rib (Fig. 11). A roentgenogram taken approximately three seconds later showed the blood again flowing past the obstruction, and an angulation of the subclavian vein as it crossed under the clavicle into the innominate vein. The zone of compression was shown by narrowing, transparency, and what seemed to be longitudinal

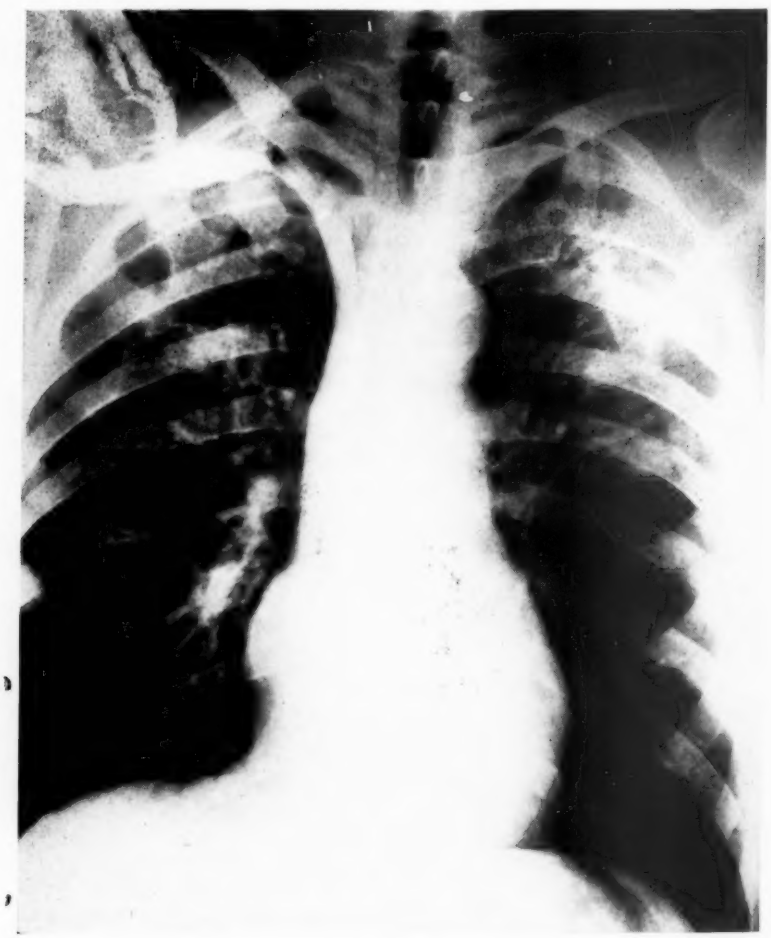

Fig. 10.—Roentgenogram in case of Robb and Steinberg, illustrating the definite indentation of the subclavian vein as it crosses the superior margin of the first rib. The clear area between the clavicle and the diodrast-filled subclavian vein probably represents the space occupied by the subclavius muscle. (Reproduced from Sampson, Saunders, and Capp.[41])

folding of the vein (Fig. 12). These two cases confirm the hypothesis offered in this paper, rather than the hypotheses offered by Lowenstein and Veal and McFetridge.

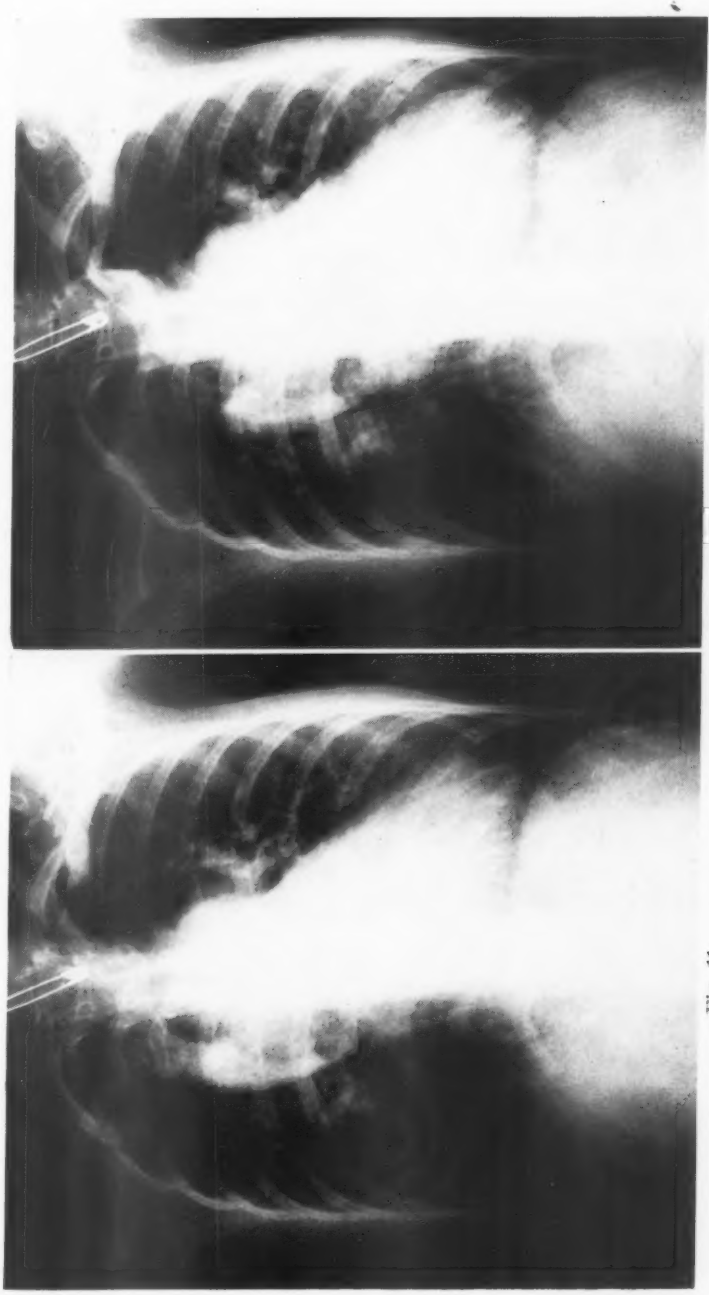

Fig. 11.

Fig. 12.

Fig. 11.—Roentgenogram taken 8 seconds after injection of diodrast, showing point of obstruction in the subclavian vein immediately proximal to its crossing of the first rib. (Reproduced from Medico-Surgical Tributes to Harold Brunn.)

Fig. 12.—Roentgenogram taken approximately eleven seconds after injection of diodrast. The blood is again flowing past the obstruction. An angulation is shown in the subclavian vein as it crosses under the clavicle into the innominate vein. (Reproduced from Medico-Surgical Tributes to Harold Brunn.)

It is the additional intention to present in this paper the possibility that the disease in all four classifications of activity may have resulted from a predisposing anatomic configuration of the clavicles and first ribs. The hypertrophy of the subclavius muscles that should occur in muscular, athletic men and women may be a contributing factor. In the numerous cases reported in the literature, no data are given to confirm this hypothesis. But in Cases 1 and 2 the characteristic rib and clavicle relations were demonstrated by physical examination and roentgenographic studies (Figs. 1, 2, 3, and 4). The routine method of taking roentgenograms of the chest was used in these two cases; this consists of having the patient extend his arms forward around the cassette, which tends to throw the shoulders forward. Thus, the roentgenograms show the clavicles in a lower position than normal, as illustrated in the photographs. Studies of chest and clavicle positions were not made in Cases 3, 4, and 5.

It is conceded that with sufficient trauma or other anatomic variation, thrombosis may occur without the causative factors presented herein.

CONCLUSIONS

1. Five cases of primary thrombosis of the axillary vein have been presented.

2. The clinical picture has been described, and these cases, as well as cases from the literature, have been classified according to types of physical activity which produce the lesions.

3. Compression of the subclavian vein, resulting in thrombosis, often may be caused by a posterior and cephalad rotation of the clavicle that narrows the space between the subclavius muscle and the superior margin of the inner third of the first rib through which the vein passes. This position of the clavicles may result from upward or backward motion of the shoulder girdle without abduction of the arm.

4. The hypothesis is presented that bodily build and posture, associated with broad, horizontally curving first ribs and posteriorly directed clavicles, predisposes to this condition, as well as to chronic compression of the subclavian vein.

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RATE OF PERIPHERAL BLOOD FLOW IN THE PRESENCE OF EDEMA

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THE effect of edema upon the rate of blood flow in the extremities has been studied by a number of investigators. Harrison and Pilcher[1] found that edema of the leg, whether caused by cardiac disease or other conditions, was accompanied by a high venous oxygen content and a low femoral arteriovenous oxygen difference. They considered their results to indicate that there is a greatly reduced consumption of oxygen by edematous tissues, and, further, that the rate of blood flow through these tissues is increased. Weiss and Ellis,[2] however, using the same method, were unable to confirm the results obtained by these workers. They observed no relationship between the degree of edema and the arteriovenous oxygen difference. Further, in the same subject the readings for the edematous lower extremity were nearly the same as those for the nonedematous upper extremity. They, therefore, interpreted their data to indicate that there is no increase in blood flow in the edematous leg.

Since the procedure used in the above investigations gave only an indirect measure of the rate of blood flow, and since the results obtained by the two groups of workers were contradictory, it was considered worth while to reinvestigate the subject, using the venous occlusion plethysmographic method.

METHOD

The study was performed upon seven patients with edema of one extremity, upon five patients with edema of both lower extremities anassociated with organic cardiac disease, and upon seven patients with edema of both lower extremities caused by chronic congestive heart failure. Blood flow readings, in c.c. per minute per 100 c.c. of limb volume, were obtained separately upon the hand, forearm, or leg, according to the technique previously described.[3] The room temperature was maintained between 25° and 27° C., and the bath temperature at 32° C. In the case of the forearm, the cuff utilized in applying the collecting pressure was wrapped around the arm just above the elbow, and, in the case of the leg, around the thigh just above the knee. With respect to the hand, the pressure was applied to the forearm, about three inches from the wrist. These steps were taken in order to minimize the possibility that, during a blood flow reading, edema fluid might be expressed from under the cuff into the portion of the limb in the plethysmograph, and thus produce an artifact. The only objection to this procedure, as compared with placing

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the cuff around the extremity immediately proximal to its insertion into the machine, is that the readings might possibly be somewhat smaller than the true blood flow value. In addition, when studying the forearm and leg, special precautions were taken with respect to the cuffs at the wrist and ankle, which were utilized in preventing arterial inflow into, and venous return from, the hand and foot, respectively, during a blood flow measurement. Since there was a possibility that the application of the arterial occlusion pressure might result in a movement of edema fluid from the wrist or ankle into the lower portion of the segment of the extremity under study, and since this might continue for some time after the step was performed, it was considered advisable to apply and maintain the pressure for at least three or four minutes before obtaining a blood flow reading.

For the group with edema of only one extremity, the results obtained on the contralateral normal limb were used as a control. In the cases of edema of both lower extremities, either because of congestive heart failure or other conditions, the data obtained on a series of ninety normal subjects, previously reported,[4] were used for a similar purpose.

Besides blood flow measurements, blood pressure, circulation time,* and venous pressure studies were made upon many of the patients.

RESULTS

The readings obtained in the first group of subjects, in which edema of only one extremity was present, are shown in Table I. In the case of D. R., the left upper extremity was moderately edematous as a result of pressure of metastatic carcinoma on axillary structures; the rate of blood flow in the edematous hand was significantly greater than on the contralateral control side. Subject B. B. presented a brawny type of edema of the left hand caused by breast neoplasm and lymphatic involvement, and again the flow was greater than on the normal side, although the difference was not as marked as in D. R. In two subjects, edema of one hand occurred in the period immediately after the onset of hemiplegia. As controls for these patients, blood flow readings were obtained in a group of ten subjects with a similar type of hemiplegia, but without edema. There was no significant difference between the rate of blood flow in the paralyzed hand and the normal hand in this group. With respect to the two subjects with edema, in one (E. D.) the blood flow in the edematous hand was definitely better than that in the contralateral side, whereas, in the other (A. A.), the figures were approximately the same for both the edematous and normal hand.

Of the two subjects whose forearms were studied, in one (E. K.) there was marked edema of the left upper extremity, but the right side was normal. This patient had definite signs of congestive heart failure, as indicated by the presence of edema of both the lower extremities, a circulation time of twenty-seven seconds, and a venous pressure (right arm) of 27.6 cm. of water. There was no explanation for the edema of the left upper extremity, but it was not regarded as a manifestation of heart failure because of the fact that it involved only one of the upper

*Circulation time measurements were performed with "Decholin," kindly furnished by Riedel-de Haen, Inc.

TABLE I

RATE OF BLOOD FLOW IN EDEMATOUS EXTREMITIES, COMPARED WITH CONTRALATERAL CONTROL SIDE

SUBJECT	INVOLVED SIDE			CONTROL SIDE			REMARKS		
	EXTREM.	VOL.	B. F.	EXTREM.	VOL.	B. F.			
D. R.	L. hand		11.6	R. hand		6.2			
B. B.	L. hand	460	5.1	R. hand	325	3.3			
E. D.	R. hand	630	16.2	L. hand	395	4.9		R. Arm	L. Arm
							Ven. pres.	10 cm.	11 cm.
							B. P.	172/110	168/112
A. A.	R. hand	486	4.9	L. hand	300	5.4			
E. K.	L. forearm	740	4.9	R. forearm	485	1.8		L. Arm	R. Arm
							B. P.	142/70	140/66
D. J.	L. forearm	740	1.7	R. forearm	420	2.0		L. Arm	R. Arm
							B. P.	142/98	150/100
W. H.	R. leg		4.0	L. leg		2.6			

B. F.—Rate of blood flow in c.c. per minute per 100 c.c. of limb volume.
Vol.—Volume of extremity in plethysmograph, only included in table in those instances in which the same length of involved and normal extremities was studied.

limbs. In any event, the rate of blood flow in the edematous forearm was definitely greater than that of the normal side. In the other subject (D. J.), brawny edema occurred in the left forearm after radical breast amputation for carcinoma; there was no significant difference in blood flow between the involved and control sides. In the last subject of this series (W. H.), the right lower extremity was moderately edematous as a result of metastasis from a prostatic carcinoma; the blood flow in the affected leg was definitely greater than that in the normal side.

In the second group of patients, edema of both lower extremities, unassociated with congestive heart failure, was present; the arm-to-tongue circulation time in each instance was within the range for normal subjects (Table II). With respect to M. W., no explanation could be offered for the moderate degree of edema of both legs, except that there was a history of thrombophlebitis twenty years previously. Both pigmentation and eczema were present in the skin, possibly as a result of venous and lymphatic involvement. In the case of E. E. and H. E., there were no signs of dietary deficiency, but both subjects admitted having imbibed large quantities of beer over a long period of time. H. W. showed all the classical signs of a nephrotic syndrome, and J. P. had a history of soft tissue abscesses for the preceding thirteen years, associated with chronic brucellosis, and was now suffering from amyloid disease.

In respect to the rate of blood flow in the edematous lower extremities in this series, examination of Table II reveals that in all instances the figures were either somewhat or definitely beyond the average range of 1.4 c.c. per minute per 100 c.c. of limb volume, σ –0.5,* observed in the control subjects.

*Standard deviation.

TABLE II

RATE OF BLOOD FLOW IN EDEMATOUS LEGS, UNASSOCIATED WITH CONGESTIVE HEART FAILURE

SUBJECT	DISEASE	BLOOD FLOW IN LEG	CIRCULATION TIME IN SEC.	BLOOD PRESSURE	REMARKS
M. W.	?	2.5	12	128/82	
E. E.	Cirrhosis of liver	2.2	12	154/56	
H. E.	Cirrhosis of liver	2.3	18		
H. W.	Nephrosis	R. 2.7 L. 3.2	12	126/74	Ven. pres. (fem. vein), 9 cm. H_2O; plasma cholesterol, 283 mg. %; serum protein, 4.0 mg. %; A:G ratio, 0.9. P.S.P., 75% excretion in 1 hr.
J. P.	Amyloidosis	2.4		132/70	Positive Congo red test. Albuminuria, casts. No hematuria.

Blood flow in c.c. per min. per 100 c.c. of limb volume.

In the third group of patients, edema of both lower extremities was associated with definite signs of chronic congestive heart failure; the arm-to-tongue circulation time was significantly increased in each instance. In two of the eight patients (H. N. and M. O.), auricular fibrillation had replaced normal sinus rhythm. Subject P. C. had mitral stenosis and congestive heart failure, and was also in the eighth lunar month of pregnancy.

TABLE III

RATE OF BLOOD FLOW IN THE EDEMATOUS LEG AND NONEDEMATOUS FOREARM OF PATIENTS WITH CHRONIC CONGESTIVE HEART FAILURE

SUBJECT	BLOOD FLOW		CIRCULATION TIME IN SEC.	REMARKS
	LEG WITH EDEMA	FOREARM		
H. N.	1.1			Auricular fibrillation
A. S.	1.9		23	
P. C.	1.4	3.4	29	Eighth lunar month of pregnancy
J. B.	2.5	1.3	47	2+ edema of leg
	1.3	1.1	39	No edema of leg
M. C.	1.7	1.2	22	
P. M.	1.2	2.0		
M. O.	1.4	1.9		Auricular fibrillation

Blood flow in c.c. per min. per 100 c.c. of limb volume.

As a whole, the blood flow readings obtained in the edematous legs in these patients (Table III) were smaller than those observed in the second group, in which the edema was of noncardiac origin. All the figures for the cardiac patients, however, fell within the range of the results obtained in the normal series (1.4 c.c., σ –0.5). The case of J. B. is of special interest, for measurements were obtained when the edema was present and again after it had disappeared as a result of

treatment. Examination of Table III reveals that the second reading in the leg was definitely less than the first; the blood flow in the nonedematous forearm was the same on the two occasions. With the exception of P. C., the measurements on the forearm in all the subjects with chronic congestive heart failure were within the normal range of 1.8 c.c. per minute per 100 c.c. of limb volume, σ –0.7. As previously stated, subject P. C. was in the eighth lunar month, and the increased circulation may have been caused by this fact, for it has been shown that, in some subjects, an augmentation in forearm blood flow may occur during the latter two trimesters of gestation.[5]

DISCUSSION

When the venous occlusion plethysmographic method is utilized in the study of the rate of peripheral blood flow in edematous extremities, certain objections can theoretically be raised. The first possibility, namely, that edema fluid might be forced into the segment of the limb under study by the application of either the venous or arterial occlusion pressure, has been adequately dealt with, we feel, by our method of placing the blood pressure cuffs. Further, any sudden increase in limb volume produced in this way could readily be identified on the record, for it would produce an abrupt change in the slope of the curve. All blood flow records which showed a sudden initial rise and then a more gradual ascent were either discarded or only the latter portion of the curve was utilized in the measurement of rate of blood flow. Another possible objection is that the presence of edema fluid might mechanically slow the rate at which the limb volume increases on application of the collecting pressure. Since the accumulation of blood takes place for the most part in the thin-walled veins, it is conceivable that edema fluid might act to prevent the rapid filling of this system and thus cause some obstruction to the continued flow of blood into the limb. This might result in obtaining a rate of blood flow which would be smaller, but certainly not larger, than that actually present.

Another factor which must be taken into consideration when comparing the peripheral circulation in an edematous extremity with that in a nonedematous one is the fact that in each case the reading is expressed as the number of c.c. of blood flow per minute per 100 c.c. of limb volume. The volume of the portion of the extremity in the plethysmograph is obtained by water displacement, and hence, in the case of the edematous limb, a considerable amount of edema fluid is included in this figure. This is clearly shown (Table I) in those instances in which the same length segment of edematous and normal extremities was included in the plethysmographs. In each case the volume of the involved limb was greater than that of the contralateral control side. If the figures for limb volume could be corrected for the inclusion of edema fluid, obviously the blood flow readings for the edematous extremities in all of our cases would become greater. It is a good possibility that the values

for the involved extremity in the case of A. A. and D. J. would, under these circumstances, be greater than those for the normal side.

Since there is a definite spread of blood flow readings in any series of normal subjects, there may be an objection to comparing the average for the group with the results obtained in a small number of patients. We do not consider this to apply, however, to the observations on the subjects with bilateral edema unassociated with chronic congestive heart failure, for, in every instance, the readings were beyond the upper range of the normal series. Besides, as in the case of the first group, correction for the factor of edema fluid in the volume of the limb would have further increased the magnitude of the blood flow readings in the edematous extremities. Whether this factor alone would have been sufficient to raise the average rate of local blood flow in the involved limb in congestive heart failure to a level above normal is difficult to state.

It would seem, then, that the peripheral circulation in an edematous extremity, unassociated with organic involvement of the heart, is, for the most part, increased, and certainly not decreased. The explanation for this observation is not clear. An elevated venous pressure is not, by itself, an important factor, for, in a number of our cases, the venous pressure was normal, and, nevertheless, the blood flow was increased. Further, it has been observed that, in pregnancy, in which a high femoral venous pressure is produced mechanically by the enlarging uterus,[6] the peripheral circulation through the leg remains within normal limits in at least the last two trimesters,[5] a period during which the venous pressure is the highest. It is generally accepted that edema fluid interferes with the normal interchange of oxygen between the blood stream and the tissues and with the removal of the various end products of metabolism. It is conceivable, then, that the anoxia resulting therefrom or the accumulation of vasodilator substances locally, or both of these factors, might be effective in producing arteriolar vasodilatation and an increase in blood flow to the part.

SUMMARY AND CONCLUSION

The peripheral circulation was studied in a series of nineteen patients who had edema in either a single upper or lower extremity or in both lower limbs. The venous occlusion plethysmographic method was used to ascertain the rate of blood flow separately in the hand, forearm, and leg.

It was found that the peripheral circulation in edematous extremities, unassociated with organic heart disease, was, for the most part, increased, and certainly not decreased. In respect to the patients with chronic congestive heart failure, the blood flow readings on the edematous limbs fell within the range of those obtained on normal subjects.

The possible circulatory mechanisms which are responsible for the changes in peripheral blood flow in edema are considered.

The authors wish to express their appreciation for the valuable assistance of Mrs. W. Littleford and Mr. J. Prince in carrying out the work.

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INVESTIGATIONS CONCERNING VITAL CAPACITY

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SINCE having been established nearly a century ago[1] as a quantitative measure of respiration, measurement of the vital capacity has found universal clinical application because of the ease with which it is done and its utility in clinical orientation, especially with regard to heart disease. Vital capacity measures the extensibility of the lungs, and is inversely proportional to the degree of engorgement of the lungs. Measurements of vital capacity enable us to estimate quantitatively the degree of pulmonary congestion, and thus, together with the other hemodynamic data, affords a clearer view of circulatory conditions. Its measurement is therefore considered indispensable in cases of heart disease.

The present study treats of some new aspects of spirometric research which have, in my experience, not only theoretical, but practical value.

According to the classical definition, the vital capacity is the volume of air, in cubic centimeters, which can be expelled by maximum expiration after maximum inspiration. For the actual study, the minimum duration of the expiration that represents the vital capacity was ascertained. In this way, two values were obtained: the vital capacity and the minimum duration of the forced expiration. Dividing the vital capacity by the number of seconds thus ascertained, we arrive at the value for the velocity of spirometric respiration. By this term we understand that quantity of air which corresponds to the average velocity of the quickest expiration.

In order to characterize more exactly the respiratory function in relation to spirometric determination of the maximum volume, I looked for, and found, by means of a manometer, another respiratory factor: the expiratory pressure. Following the definition of vital capacity, I ascertained the maximum pressure which the subject will generate when exhaling into a manometer after having inhaled as deeply as possible. The altitude of the mercury column represents the maximum expiratory pressure. Thus the maximum volume and pressure during maximum inspiration and expiration were ascertained.

METHOD

The vital capacity was measured with Barnes' dry spirometer, with the patient standing. At least two measurements were made, and the larger or largest was taken. After a five minutes' rest, the minimum duration of maximum expiration was measured in the following way: The subject, who has been instructed, after comfortably completing the deep inspiration, exhales as rapidly as possible, and care is taken that, during the violent expiration, no air escapes at the sides of the

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mouthpiece. The physician, chronometer in hand, observes attentively the index tube of the spirometer. He takes note of the instant when the tube indicates the entrance of the air in the spirometer, and stops the chronometer when the upward movement of the index tube has reached its end. In general, increasing the velocity of expiration does not depress the numerical value of the vital capacity. The differences between the spirometric quantities, as measured when taking into account the time factor and measured without doing so, must not exceed 100 or 200 c.c. If this should not be the case, despite a reasonable rest, the measurements must be repeated.

In any case, two measurements are made. To ascertain the velocity of the spirometric expiration, the one is utilized that takes the least amount of time, the respiratory volumes being equal, or the one that exhibits, for the vital capacity, the value nearest the one previously established.

The expiratory pressure was measured with the Baumanometer (portable or wall model) in the following way: The cuff connection of the apparatus was joined to a rubber tube 50 cm. long, identical with that used in the spirometer. The subject was instructed to inhale as deeply as possible, and then to exhale into the tube of the manometer violently, so that the mercury column of the apparatus would rise as far as possible. The subjects were standing during this procedure. Although this has been done on hundreds of patients, and marked elevations in the intrapulmonary pressure have been observed, no accident whatever has happened, either to healthy or ill persons; this is in contradistinction to cases in which Bürger's[4] test was applied. As to the usual complaint about congestion in the head, felt in different degrees from a slight ache to giddiness, it can be stated that these symptoms will completely disappear in a few minutes.

RESULTS

Healthy Persons (Table I).—In a group of thirty healthy persons whose ages varied between 15 and 54 years, the results were as follows: The average vital capacity was 4600 c.c., with variations between 5500 and 4000 c.c., which figures, although they were not related to the surface area of the body, are normal. The minimum time for exhaling the vital capacity volume was, on an average, 3.4 seconds, with a range from 4.2 to 2.9 seconds. The velocity of spirometric respiration was, on the average, 1340 c.c., and individual values varied between 1660 and 1110 c.c. The average maximum expiratory pressure was 119 mm. Hg, and the range was from 180 to 86 mm.

The possibility of a correlation between the fundamental respiratory factors led to an inquiry into the behavior of the vital capacity in relation to the expiratory pressure, using correlation indexes. Since the correlation index showed variations between 59.5 and 30.4, i.e., a difference of 100 per cent, it became evident that there was no intimate relation between the vital capacity and the expiratory pressure. These two factors are independent of each other. It is true that in cases of large vital capacity the expiratory pressure is often high, and vice versa, but there is no constant relation. On the other hand, the velocity of spirometric respiration does exhibit a rather constant correlation with the absolute value for the vital capacity, as well as with the expiratory pressure. The correlation index, Vel./V.C., averaging 0.2, covers variations not exceeding 31 per cent (0.35 to 0.24). Similar constancy pre-

TABLE I

NORMAL PERSONS

NO.	AGE (YR.)	VITAL CAPACITY (C.C.)	EXPIR. TIME (SEC.)	EXPIR. VELOCITY (C.C. PER SEC.)	EXPIR. PRESSURE (MM. Hg)	V.C. / P.	VEL. / V.C.	VEL. / P.
1	29	5500	3.9	1400	138	39.3	0.25	8.8
2	25	5500	3.7	1380	115	47.8	0.25	12.0
3	25	5300	3.6	1470	135	39.2	0.28	10.9
4	39	5200	3.4	1500	170	30.5	0.29	8.8
5	27	5100	3.0	1660	143	35.7	0.33	11.6
6	24	5100	3.0	1660	140	36.4	0.33	11.8
7	54	5000	3.0	1600	180	27.8	0.33	8.8
8	24	5000	3.5	1400	110	45.4	0.28	12.6
9	19	4800	4.0	1200	110	43.6	0.25	10.9
10	34	4800	3.6	1280	90	53.3	0.28	14.2
11	42	4700	3.6	1350	120	39.1	0.28	11.2
12	18	4700	3.5	1200	115	40.8	0.21	10.4
13	42	4700	4.1	1130	95	59.5	0.24	11.8
14	24	4600	4.0	1150	110	41.8	0.25	10.4
15	35	4500	3.0	1480	130	34.6	0.33	11.4
16	38	4500	4.2	1350	95	40.7	0.24	14.2
17	28	4500	3.6	1236	86	52.3	0.28	14.3
18	26	4400	3.4	1400	145	30.4	0.29	9.7
19	36	4400	3.0	1400	138	31.9	0.33	10.1
20	35	4300	3.4	1260	125	34.1	0.29	10.0
21	39	4300	3.6	1140	100	43.0	0.28	11.4
22	41	4300	3.7	1110	100	43.0	0.25	11.1
23	28	4200	3.2	1250	120	33.6	0.31	10.4
24	32	4200	2.9	1410	120	35.0	0.34	11.7
25	28	4200	2.8	1520	120	35.0	0.35	12.6
26	15	4100	3.7	1110	105	39.0	0.27	10.6
27	38	4000	3.1	1280	110	36.3	0.32	11.6
28	37	4000	2.9	1350	110	36.3	0.34	12.2
29	32	4000	3.2	1270	105	38.1	0.31	10.1
30	39	4000	3.1	1290	90	44.4	0.32	14.3
Average	31.8	4600	3.4	1340	119.0			

V. C. = Vital capacity.
Vel. = Velocity.
P. = Pressure.

vails in the index, Vel./Exp. Press., which averages 11.3. It covers a range of 39 per cent, and its extremes are 14.3 and 8.8.

All this can be summed up as follows: The respiratory velocity is a function of the vital capacity as well as of the expiratory pressure, i.e., it is in direct proportion to them.

Clinical Application.—To study the characteristics of diminution of the vital capacity from various causes (cardiac and pulmonary), patients with severe heart failure and others with bronchial asthma and emphysema, without heart failure, were chosen. The ten cardiac patients (Table II) had severe congestive failure, although with different degrees of dyspnea, cyanosis, edema, and engorgement (pulmonary, hepatic). They were, on an average, 50.6 years of age. The vital capacity averaged 1630 c.c., but, in an extreme case, it was reduced to as little as 600 c.c. The velocity of expiration was 3.4 seconds, which was the same as that of the healthy persons; but, since cardiac patients

TABLE II

DECREASED VITAL CAPACITY AS A RESULT OF HEART FAILURE

NO.	AGE (YR.)	VITAL CAPACITY (C.C.)	EXPIR. TIME (SEC.)	EXPIR. VELOCITY (C.C. PER SEC.)	EXPIR. PRESSURE (MM. Hg)	CLINICAL DIAGNOSIS
1	40	1300	2.4	540	45	Decomp. aortic insufficiency
2	60	2100	5.0	425	45	Decomp. mitral disease
3	39	1300	3.0	430	50	Decomp. aortic insufficiency
4	64	2200	3.6	610	50	Decomp. arteriosel. heart dis.
5	56	1800	3.9	460	65	Decomp. hypertens. heart dis.
6	44	600	2.0	300	70	Decomp. mitral disease
7	56	2000	3.1	630	70	Decomp. arteriosel. heart dis.
8	42	2100	2.6	800	70	Decomp. hypertens. heart dis.
9	52	2100	5.0	410	70	Decomp. hypertens. heart dis.
10	53	800	2.9	275	70	Decomp. aortic insufficiency
Average	50.6	1630	3.4	488	61	

with congestive failure need the same time as healthy persons to exhale their reduced vital capacity volume, which is only one-third of that of the healthy persons, that value means nearly a tripled duration of expiration, and the fact that the velocity of spirometric expiration averaged 488 c.c. per second is in perfect accord with this.

The most important abnormality was in the expiratory pressure. It was reduced to 45 mm. in the extreme cases, and averaged 61 mm., or half of the normal value. There was no correlation between the vital capacity, rate of expiration, expiratory velocity, and expiratory pressure. Individual factors accounted for the respective values.

TABLE III

DECREASED VITAL CAPACITY CAUSED BY PULMONARY DISEASE

NO.	AGE (YR.)	VITAL CAPACITY (C.C.)	EXPIR. TIME (SEC.)	EXPIR. VELOCITY (C.C. PER SEC.)	EXPIR. PRESSURE (MM. Hg)	CLINICAL DIAGNOSIS
1	43	2000	4.0	500	130	Emphysema, chronic bronch.
2	62	1200	3.2	370	125	Emphysema, chronic bronch.
3	47	2200	4.6	480	120	Asthma
4	53	2100	3.1	670	120	Asthma
5	56	1200	3.6	280	115	Asthma
6	60	1000	2.8	350	110	Asthma
7	56	600	6.4	94	100	Emphysema, chronic bronch.
8	45	1100	6.1	180	100	Asthma
9	60	2000	3.7	540	100	Asthma
10	50	2400	3.6	660	100	Emphysema, chronic bronch.
Average	52.6	1580	4.1	412	112	

The ten patients with decreased vital capacity as a result of pulmonary disease (Table III) were nearly of the same age as the cardiac patients, i.e., 52.6 years. They exhibited a still more marked diminution of the vital capacity (average, 1580) but, on the other hand, the expiratory velocity averaged 4.1, which value indicated slower exhalation in accordance with the average value for the velocity of spirometric

respiration, i.e., 412 c.c. per second. With respect to the alterations of vital capacity and duration and velocity of expiration, these patients showed changes similar to (but more marked than) those of the cardiac patients, but the behavior of the expiratory pressure was very different; i.e., it was normal or only slightly reduced (average value, 112mm.).

Combination of the spirometric data with measurements of the respiratory pressure allows us to reach an objective differential diagnosis of the causes of reduced vital capacity, either cardiac or pulmonary. A normal or slightly decreased expiratory pressure indicates a pulmonary origin, whereas a marked diminution of the pressure is characteristic of cardiac disease.

By applying the procedure described above to typical cases of either pulmonary or cardiac disease, it was possible not only to establish the alterations characteristic of either, but also to make an etiopathologic analysis of the intervening factors in cases in which pulmonary and cardiac diseases coexisted.

TABLE IV

MISCELLANEOUS CASES

NO.	AGE (YR.)	VITAL CAPACITY (C.C.)	EXPIR. TIME (SEC.)	EXPIR. VELOCITY (C.C. PER SEC.)	EXPIR. PRESSURE (MM. Hg)	DIAGNOSIS AND CLINICAL CONDITION
1	28	700	4.0	175	80	Asthma with slight cardiac decompensation
2	58	800	3.0	260	70	Hypertension, chronic bronchitis, slight decompensation
3	69	2100	4.3	490	85	Emphysema, slight decompensation
4	41	3100	3.4	930	115	Bronchial asthma in free interval
5	50	3100	3.1	1000	110	Bronchial asthma in free interval
6	62	1100	3.6	300	85	Emphysema, marked decompensation
7	32	1500	2.6	570	110	Mitral stenosis and insufficiency, decompensated
8	47	4200	3.5	1170	170	Aortic insufficiency, perfectly compensated
9	49	4000	3.4	1170	140	Mitral disease, perfectly compensated
10	15	3700	3.0	1190	110	Aortic insufficiency, perfectly compensated

Table IV gives data on ten complex cases. The first patient suffered from bronchial asthma. He was examined during an attack. This case was characterized by a relatively low expiratory pressure, indicating some kind of heart failure. The patient had a symptom of slight heart failure, namely, fatigability, even apart from the attacks. His heart was slightly enlarged, especially the right auricle and ventricle. T_2 and T_3 of the electrocardiogram were nearly isoelectric, indicating myocardial damage. In short, his disease was mainly pulmonary, without excluding cardiac affection.

Case 2 was similar in every respect.

In Case 3 the patient showed electrocardiographic alterations suggestive of damage of the myocardium, a moderate diminution of the vital capacity, slow expiration, and a moderate decrease in the expiratory pressure, indicating cardiac disease.

In Case 6 the situation was the same, except that the pulmonary factor was more marked.

In Cases 4 and 5 (bronchial asthma, in free interval) there was no heart disease, for the vital capacity was only moderately decreased, the expiratory pressure was normal, and the expiratory velocity was nearly normal.

In Case 7 the patient had a valvular lesion and heart failure, with marked dyspnea and edema, but, as a discordant factor, a normal expiratory pressure. This is certainly not frequent, and must be explained in the following way: The patient, when in a state of perfect compensation, must have had an elevated expiratory pressure. His actual pressure, although apparently relatively normal, was already a reduced pressure which would sink still lower if the heart failure were to continue.

In Cases 9 and 10, the patients were suffering from valvular lesions, but had no heart failure. It is striking that these patients should respond normally, although their expiratory pressures were clearly higher than normal.

TABLE V

PSEUDONORMAL VITAL CAPACITY

NO.	AGE (YR.)	VITAL CAPACITY (C.C.)	EXPIR. TIME (SEC.)	EXPIR. VELOCITY (C.C. PER SEC.)	EXPIR. PRESSURE (MM. HG)	DIAGNOSIS AND CLINICAL CONDITION
1	53	4000	5.9	670	75	Arteriosclerotic heart disease, compensated.
2	65	3700	4.1	900	80	Arteriosclerotic heart disease, slight decompensation.
3	45	3600	4.6	780	60	Aortic insufficiency, myocardial lesion, slight decomp.
4	44	3500	7.5	460	95	Silicosis.
5	50	3100	4.6	750	60	Mitral and aortic insufficiency. Slight decompensat.
6	60	3300	4.9	680	80	Arteriosclerotic heart disease, myocardial damage.
7	42	3300	4.0	820	70	Myocardial degeneration.
8	45	3200	8.4	360	60	Aortic aneurysm, myocardial damage.
9	50	3100	3.6	830	65	Myocardial degeneration.
10	65	3100	5.4	570	80	Hypertension, slight decompensation.

Table V presents data on patients with pseudonormal vital capacity. Although these persons had a normal vital capacity, the symptoms and signs indicated marked pathologic alterations. It is in these cases that the results of the spirometric and clinical examination contradict each other. But, on investigating the respiratory velocity and the expiratory pressure, we find that, behind the normal vital capacity, a pathologic situation is hidden. Thus it is that, by deeper investigation of the respiratory function, we recognize the real situation in cases in which, in spite of the apparently pathologic state, the vital capacity could be classified as normal.

DISCUSSION

In general, the following functional factors determine the numerical value of the vital capacity: (1) the cardiac factor, (2) the pulmonary factor, (3) the muscular factor, and (4) the psychological factor.

The cardiac factor has to do with the blood volume in the lungs. Pulmonary engorgement increases the blood pressure in the pulmonary circulation and, with the help of changes in intrapulmonary gas pressure, biochemical alterations, and alterations in the capillary permeability, produces pulmonary edema and a diminution in the air volume of the lungs.

The pulmonary factor embraces pulmonary elasticity and the amount of functioning alveolar membrane, both of which may be reduced by emphysema or disease of the parenchyma itself.

Although, under normal conditions, expiration is a passive act, forced expiration, or expiration against resistance, is the result of a muscular effort in which all the expiratory muscles, normal and auxiliary, participate. Therefore, the vital capacity may be decreased through muscular insufficiency, although, properly speaking, no abnormalities either of the circulation or of respiration exist. This occurs in cases of Addison's disease, Graves' disease,[2] and myxedema. The muscular factor also plays an important role in diminution of the vital capacity caused by cardiac disease. Psychic factors, such as will power, spirit of cooperation or competition, or vanity provoked by indifference, may modify the vital capacity.

Although there are abundant physiologic and clinical observations on vital capacity, not many measurements of the pressure generated during forced expiration have been made. On measuring the maximum expiratory pressure in three persons, Senner[3] found a range from 50 to 120 mm. Hg, and Bürger[4] states that the maximum value for healthy persons is about 140 mm. Hg.

My studies indicate that healthy persons can produce, on the average, a pressure of 119 mm.; this implies an ample range of higher values, but a narrow range of lower ones. The pressure during maximum expiration does not depend on the vital capacity, but is related to the

strength of the expiratory muscular apparatus. Henderson,[8] Eppinger,[5] and Budelmann[6] have, by direct measurements, observed the diminution in the tonicity of muscles in cases of cardiac insufficiency. To explain the diminution in vital capacity in cases of infection, Pries[7] has accepted Eppinger's theory that, in serous inflammation, the cause is an alteration in capillary permeability, which may produce a diminution in the tonicity of the muscular apparatus. The latter is directly responsible for the diminution in the vital capacity. The decrease in the expiratory pressure in cases of cardiac insufficiency illustrates again the often observed fact that there is diminished tonicity of the muscles in such cases. In absolute conformity with clinical observations regarding the strength of the respiratory muscular apparatus in cases of asthma or emphysema, not complicated by heart failure, the maximum expiratory pressure is normal, in spite of factors which tend to obstruct expiration.

CONCLUSIONS

1. A new spirometric procedure of investigating the respiratory function, that adds to the factor of volume those of time and pressure, is described.

2. By measuring at the same time as the vital capacity the minimum duration of the quickest possible exhalation of a volume equal to the vital capacity, we obtain the velocity of spirometric respiration by dividing the vital capacity by the expiration time. The velocity of spirometric respiration is that air volume that enters the spirometer per second. It represents the average of the quickest possible expiration. Furthermore, the maximum expiratory pressure is measured; this corresponds to the respiratory movement, and is, in a sense, identical with the vital capacity.

3. The standard values for healthy persons for each of the respiratory factors, as well as the correlations between them, are established. There is no relation between the vital capacity (volume) and the expiratory pressure (strength), i.e., they are independent of each other, whereas the velocity of spirometric respiration depends on the vital capacity, as well as on the expiratory pressure.

4. Any decrease in vital capacity that is caused predominantly by cardiac disease is characterized by prolongation of the expiration time, decrease in the velocity of spirometric expiration, and, above all, by a marked decrease in the expiratory pressure that, in typical cases, sinks below half the standard value.

5. Decreases in vital capacity that are caused primarily by pulmonary disease are characterized by a more marked prolongation of expiration time, by a distinct decrease in the velocity of respiration, and, most of all, by the fact that the expiratory pressure is normal or hardly altered.

6. The decrease in expiratory pressure in cases of cardiac insufficiency is explained by a diminution in the strength of the respiratory muscular apparatus.

7. The diagnostic signs (spirometric data) relating to the specific differences between diminution of vital capacity caused by cardiac and pulmonary diseases are established, and the concept of pseudonormal vital capacity is defined.

8. The fact that a person has a normal vital capacity does not prove that he has a normal respiratory function. Other factors, such as time, velocity, and expiratory pressure, must be considered.

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THE EFFECT OF THE INTRAVENOUS ADMINISTRATION OF LANATOSIDE C UPON THE OUTPUT, DIASTOLIC VOLUME, AND MECHANICAL EFFICIENCY OF THE FAILING HUMAN HEART*

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DURING a study of the response of patients with heart failure and normal sinus rhythm to the intravenous administration of lanatoside C,[1] it was noted that the volume of the pulse increased within thirty minutes after injection of the drug. Subsequent observation showed that this alteration in pulse volume was associated with an elevation of pulse pressure, a decrease in the circulation time, and sometimes with a significant drop in the venous pressure within one-half to two hours after administration of the drug. Since an increase in cardiac output might well account for these phenomena, it was decided to check this function and other circulatory measurements before and after the intravenous administration of lanatoside C‡ to patients with severe heart failure and normal sinus rhythm.

When the action of a digitalis glycoside is studied in the laboratory on an experimental animal, a mercury manometer is used to measure the systolic and diastolic blood pressure in the carotid artery; a cardiometer is fitted over the ventricles in order to ascertain the systolic and diastolic heart volumes (the difference between the two is equal to the sum of the output of the left and right ventricles); a stromuhr records the volume of blood flow; and the venous pressure in the right auricle is measured with a water manometer.

In investigating the effect of lanatoside C upon a Starling heart-lung preparation,[2] we noted that the addition of a little chloroform to the air which is going to the lungs of this preparation causes the heart to dilate and the venous pressure in the left and right auricles to rise. The blood pressure remains constant because of the constant resistance in the system, and the stroke and minute output may remain the same or decrease moderately. (This experiment is the paradigm of acute heart failure of moderate degree.) If lanatoside C is now added to the blood leaving the venous reservoir, the dilatation of the heart soon disappears, the venous pressure falls to normal, and the output of the

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heart increases. If large amounts of chloroform are taken up by the blood passing through the lungs, much greater dilatation is produced, the venous pressure rises markedly, and the cardiac output decreases materially. (This represents acute heart failure of high degree.) In such a preparation the addition of lanatoside C to the circulating blood usually causes some decrease in the diastolic volume of the dilated heart and in the venous pressure. If the cardiac output has been markedly reduced, it may or may not increase after the lanatoside has been added; rarely will it return to the previous normal value.

Experimental studies of the effect of digitalis upon the output of the heart depend upon the state of that muscle when the drug is given. Schweigk[3] showed that the hypodynamic frog heart responds to the administration of digitalis lanata with an increase in minute volume. Similarly, failing heart-lung preparations of both cats and dogs respond to digitalis with an increase in the cardiac output and a decrease in the heart volume. Bijlsma and Roessingh[4] and Plant[5] found that strophanthin diminished the size and increased the stroke output of failing hearts which had been poisoned with chloral hydrate or phosphorus. Similar observations have been reported by Cohn and Steele[6] and by Anitschow and Trendelenburg.[7] Peters and Visscher[8] and Moe and Visscher[9] have demonstrated that digitalis and lanatoside C increase the mechanical efficiency of a failing heart-lung preparation. In these investigations the work of the heart was kept constant, and it was noted that the administration of the cardiac glycoside produced a decrease in the diastolic volume of the heart and a diminution of its oxygen consumption per gram meter of cardiac work. Such experiments prompted us to study, in man, changes in cardiac output, diastolic heart volume, venous pressure, work of the heart, etc., after the intravenous administration of lanatoside C.

Reports on the action of cardiac glycosides upon the stroke output of the human heart in the presence of failure are contradictory. Some investigators have found that the minute volume was increased, others have reported that it was decreased, and some could detect no change. Stewart and his co-workers,[10] using the Grollman acetylene technique[11] for measurement of the cardiac output, found an increase in cardiac output and a decrease in the area of the roentgenographic shadow of the heart. Grassmann and Herzog[12] followed changes in the stroke output of the hearts of decompensated patients who received strophanthin, intravenously, using both the acetylene technique and the method of Broemser and Ranke.[13] In many instances they noticed an increase in cardiac output within fifteen minutes after injection of the drug.

Harrison and his associates,[14] however, failed to secure consistent results with the Grollman method. McGuire, Hauenstein, and Shore,[15] who employed both the direct Fick[16] and the Grollman technique, also found that the effect of digitalis upon the cardiac output was variable.

In our opinion, the actual stroke output of the left ventricle cannot be measured accurately by the Grollman technique, or even by the direct Fick method if aortic or mitral insufficiency is present. These procedures measure only the amount of blood that moves onward in the aorta. The methods of Broemser and of Bazett, et al.,[17] measure the output of blood from the left ventricle in the presence of aortic insufficiency, but do not account for all the blood pumped by the left ventricle when there is mitral insufficiency. It is possible that some mitral regurgitation may occur in many cases of heart failure associated with dilatation of the left ventricle, and the methods just mentioned will not measure ventricular output accurately in such instances.

Keys and Friedell[18] have perfected an ingenious method of ascertaining cardiac output from roentgenkymographic measurements. Configurations of the heart during systole and diastole are traced from the roentgenkymograms, and the diastolic and systolic areas are then measured with a planimeter. The diastolic and systolic volumes of the heart can be computed from the planimetric measurements by means of the Keys and Friedell formula. The difference between the diastolic and systolic volumes is an index of the cardiac output.

The teleoroentgenkymogram supplies data analagous to those secured from cardiometer tracings of the heart-lung preparation, for both measure changes in systolic and diastolic heart volume. Measurements of venous and arterial pressure in man are comparable to those of right auricular and aortic pressure in the heart-lung preparation. The work done by a heart-lung preparation can be computed for any given period from the product of the stroke output times the mean blood pressure. In man, measurement of the work of the left ventricle in gram meters can be calculated by multiplying the stroke output by the mean blood pressure.

The diastolic volume of normal and pathologic hearts can be ascertained accurately by the roentgenkymographic method of Keys and Friedell, but the true systolic volume cannot be ascertained by this method because the roentgenkymograph records the shortening of cardiac diameters only in the transverse direction, and not in the sagittal. For this reason, the difference between the diastolic volume and this modified systolic volume turns out to be approximately the output of one ventricle, rather than of two. Keys' formula will give accurate values for the cardiac output of one ventricle of the average normal heart, but it cannot be said that this formula will accurately estimate the cardiac output of one ventricle in all types of heart disease. However, the teleoroentgenkymogram does show the increase in cardiac output associated with aortic and mitral regurgitation which the foreign gas methods cannot measure. In our experiments we used the technique described by Keys and Friedell because we hoped to measure the changes in both the diastolic heart volume and cardiac output after the intravenous administration of lanatoside C.

Increases or decreases in the diastolic volume of the heart are important because, as Starling and Visscher[19] and Hemmingway and Fee[20] have demonstrated, the oxygen consumption of the heart muscle is directly proportional to its diastolic fiber length. From measurements of the oxygen consumption of the heart and the actual work done by the heart, its mechanical efficiency can be computed. When there is cardiac enlargement, the stroke volume of the left ventricle, as obtained by the Keys and Friedell formula, may not be numerically exact, but changes in the amplitude of cardiac contraction in the transverse direction are obvious at a glance (Figs. 1, 2, 3). Any change in the outline of the cardiac border in the frontal plane must be accompanied by comparable changes in its sagittal dimensions, and hence successive output estimations from kymograms should be reliable indices of the direction (sense) and magnitude of any change in the output of the heart. If

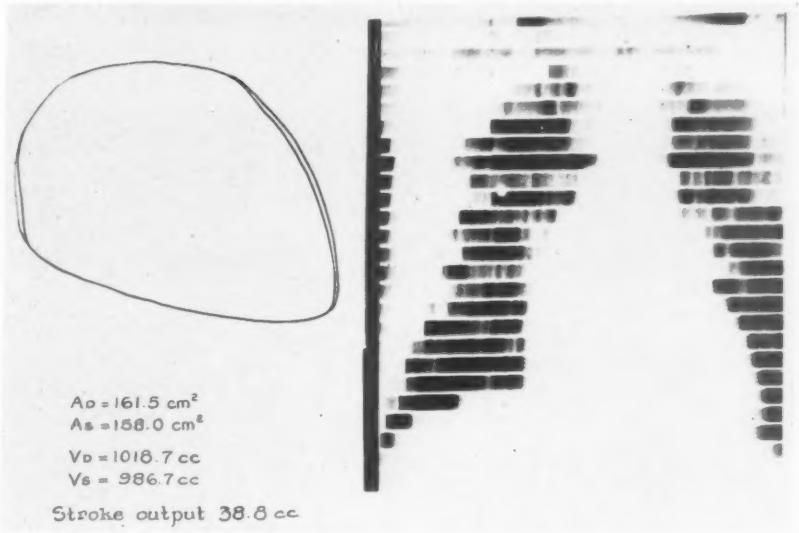

Fig. 1.—Roentgenkymogram of R. A. and derived planimeter tracings of the systolic and diastolic heart areas before the intravenous injection of lanatoside C.

the calculated work of the left ventricle increases while its diastolic volume decreases or remains the same, it is reasonable to assume that the oxygen consumption has not increased, and, therefore, this increase in work represents an improvement in mechanical efficiency.

For our study of cardiac output, ten patients with severe congestive failure (Class 3) and normal sinus rhythm were given two to eight days' preparatory rest in bed, with the fluid intake restricted to 800 c.c. daily. Daily measurements of venous pressure, vital capacity, apical rates, etc., were recorded on individual charts, and the cyanide or decholin circulation time, and blood pressure, were taken frequently. All measurements were again secured shortly before the first teleoroentgen-

kymogram was made. Then 8 c.c.* of lanatoside C were given intravenously, and the measurements were repeated at 5- to 10-minute intervals. A second kymogram was taken thirty minutes to two hours after injection of the drug, depending upon the response of the patient.

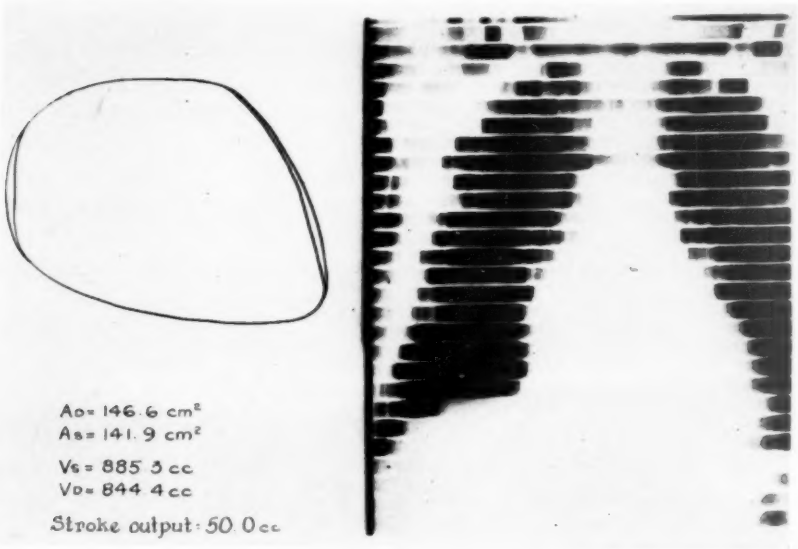

Fig. 2.—Roentgenkymogram of R. A. and derived planimeter tracings of the systolic and diastolic heart areas 2 hours after the intravenous injection of lanatoside C.

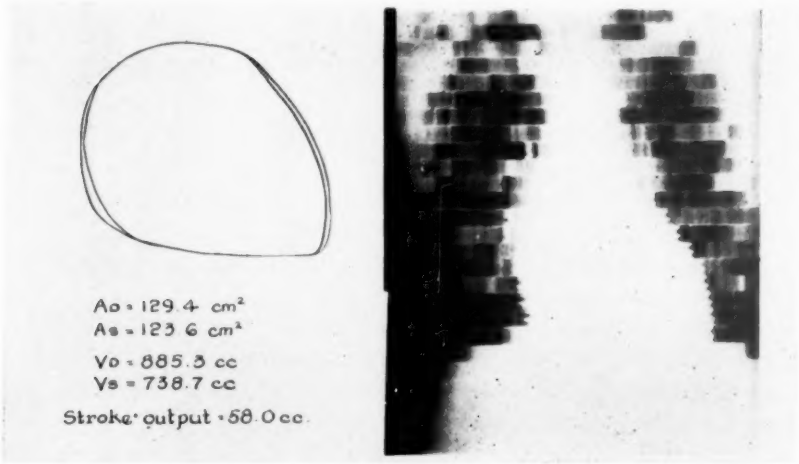

Fig. 3.—Roentgenkymogram of R. A. and derived planimeter tracings of the systolic and diastolic heart areas 19 days after the intravenous injection of lanatoside C.

Table I presents average values of the clinical and kymographic measurements before and after the administration of lanatoside C, and

*Each cubic centimeter of solution contains 0.20 mg. One Hatcher-Brody cat unit is contained in approximately 0.25 mg. of the drug.

TABLE I

AVERAGES OF THE CIRCULATORY MEASUREMENTS MADE ON TEN PATIENTS BEFORE THE INTRAVENOUS INJECTION OF LANATOSIDE C, TWO HOURS AFTER THE INJECTION, AND, IN 7 CASES, AT THE TIME OF DISCHARGE. TWO PATIENTS WERE RESTUDIED 3 AND 13 MONTHS, RESPECTIVELY, AFTER THE INTRAVENOUS INJECTION OF LANATOSIDE C

TIME	PULSE PRESS.	CIRC. TIME	VEN. PRESS.	DIAST. HT. VOL. IN C.C.	STROKE OUTPUT	MIN. VOL.	WORK PER BEAT IN GM. MTRS.	NO. OF CASES
Before Lanatoside C	45.2	34.0	20.3	1021	44.4	4.2	67.6	10
½-2 hr. after Lanatoside C	*73.3	*26.6	*15.0	986	54.6	5.0	*94.7	10
At discharge	*76.2	*30.0	*6.2	*755.5	55.8	4.3	*94.0	7
3-13 months later	73.0	21.05	6.5	691	58.2	4.8	102	2

*Starred numbers represent average values which have been shown by statistical analysis (the "t" test) to be significantly different from average values obtained from measurements taken at the start of the experiment. Values for the two patients restudied three and 13 months later were not analyzed.

shows the trend of reaction in the ten patients. The pulse pressure usually rose, the circulation time and venous pressure decreased, and the stroke and minute output rose slightly. The work of the heart increased while the diastolic volume decreased slightly, indicating a corresponding improvement in mechanical efficiency.

Table II presents individual data for each patient and affords a more accurate appraisal of our results. In eight of the ten patients there was an increase of 30 to 140 per cent in the stroke output of the heart; this was associated with work increments of 30 to 130 per cent, while the size of the heart remained unchanged or decreased. Consequently, these eight patients exhibited a definite improvement in the mechanical efficiency of the heart within 30 to 120 minutes after the injection of 8 c.c. of lanatoside C. In the other two patients the changes were slight, but in both the minute volume of the heart was so large before the administration of lanatoside C that no great increase was to be expected after giving the glycoside.

Roentgenkymographic output studies on seven patients (who received maintenance doses of 1 to 5 tablets* of lanatoside C daily) were repeated three to six weeks after the intravenous injection of the drug. Data obtained at this time are presented in Table III. There was no significant increase in the average stroke output, but the average diastolic heart volume had decreased more than 200 c.c. This represents a further improvement in the mechanical efficiency of the hearts of these patients, for the hearts were doing approximately the same amount of external work with a diminished diastolic volume, and hence with less oxygen consumption. In other words, these hearts were utilizing considerably smaller quantities of energy to perform the same external work.

*The tablets used in this study contained 0.25 mg.

TABLE II

INDIVIDUAL CIRCULATORY MEASUREMENTS BEFORE, AND 1½ TO 2 HOURS AFTER, THE INTRAVENOUS INJECTION OF LANATOSIDE C

TIME	BL.P.	P.P.	H.R.	C.T.	V.P.	D.H.V.	S.O.	M.O.	P.P. × H.R.	WORK/ BEAT
	C. H.		*Coronary Disease*							
1:20 p.m.	132/84	48	96	28	21	1068	66.0	6.2	4,608	95
2:12	Injection 8 c.c. lanatoside C									
4:13	134/80	54	92	25	7.5	1007	57.0	5.3	4,968	84
% Increase		12%		-11%		-6%	-14%	-15%	8%	-12%
	Inconclusive 2 hours after injection									
	C. F.		*Hypertension and Coronary Disease*							
8:40 a.m.	120/96	24	96	46	22	973	24.0	2.3	2,300	35
9:30	Injection 8 c.c. lanatoside C									
10:30	158/100	58	90		12	833	32.2	2.9	5,200	57
% Increase		140%				-14%	34%	26%	126%	62%
	Mechanical efficiency increased more than 75%									
	J. B.		*Syphilitic Aortitis, Aortic Insufficiency*							
3:00 p.m.	170/96	74	92	42.5	27	1168	30.6	2.8	6,808	54
3:10	Injection 8 c.c. lanatoside C									
4:20	196/76	120	92	24.7	19	1211	70.2	6.5	11,040	131
% Increase		62%		42%		4%	130%	132%	62%	142%
	Mechanical efficiency increased 138%									
	J. H.		*Hypertension and Coronary Disease*							
3:40 p.m.	134/94	40	102	38.2	24	1016	47.6	4.9	4,080	74
3:45	Injection 8 c.c. lanatoside C									
4:35	160/98	62	100	29.4	20	1044	59.2	6.0	6,200	105
% Increase		55%		23%		3%	24%	22%	52%	42%
	Mechanical efficiency increased 39%									
	A. C.		*Syphilitic Aortitis, Aortic Insufficiency*							
1:55 p.m.	144/108	36	100	26.2	18	1060	38.2	3.8	3,200	65
2:05	Injection 8 c.c. lanatoside C									
3:30	182/112	70	88	16.2	12	1046	51.2	4.5	6,160	102
% Increase		94%		38%		-2%	34%	18%	92%	54%
	Mechanical efficiency increased 59%									
	R. A.		*Syphilitic Aortitis, Aortic Insufficiency*							
2:15 p.m.	132/60	72	104	35.9	19	1019	38.8	4.0	7,488	52
2:30	Injection 8 c.c. lanatoside C									
3:00	154/56	98	104	24.5		885	50.0	5.2	10,192	74
% Increase		36%		-32%		-13%	29%	30%	36%	42%
	Mechanical efficiency increased more than 55%									
	H. S.		*Hypertension and Coronary Disease*							
2:00 p.m.	126/108	18	108	26	14	1042	51.0	5.5	1,944	81
2:15	Injection 8 c.c. lanatoside C									
3:15	144/98	46	107	20.4		1025	49.0	5.2	4,922	80
% Increase		155%		20%		-1.5%	-4%	-6%	153%	-1%
	Inconclusive 1 hour after injection									

Bl.P.—Blood pressure in mm. Hg
P.P.—Pulse pressure in mm. Hg
H.R.—Heart rate per minute
C.T.—Circulation time in seconds
V.P.—Venous pressure in cm. of water
D.H.V.—Diastolic heart volume in c.c.
S.O.—Stroke output in c.c.
M.O.—Minute output in liters
P.P. × H.R.—Pulse pressure times heart rate
Work/beat—Mean blood pressure times stroke output in gram meters

TABLE II—CONT'D

TIME	BL.P.	P.P.	H.R.	C.T.	V.P.	D.H.V.	S.O.	M.O.	P.P. × H.R.	WORK/ BEAT
	H. J.		*Coronary Arteriosclerosis*							
2:50 p.m.	90/76	14	90		18	1015	48.0	4.3	1,260	54
3:00	Injection 8 c.c. lanatoside C									
3:15	110/84	26	92			1044	59.0	5.4	2,392	77
% Increase		85%				3%	23%	25%	90%	43%
	Mechanical efficiency increased 40%									
	F. S.		*Hypertension and Coronary Disease*							
2:00 p.m.	108/82	26	104	59.2	21	997	37	3.8	2,704	47
2:10	Injection 8 c.c. lanatoside C									
2:45	160/100	60	98	33.2	22	873	46	4.5	5,880	81
% Increase		140%		44%		-13%	24%	18%	117%	72%
	Mechanical efficiency increased more than 85%									
	L. P.		*Hypertensive Heart Disease*							
9:40 a.m.	190/90	100	77	25.9	9	849	63	4.8	7,700	119
10:01	Injection 8 c.c. lanatoside C									
10:36	236/80	156	62			792	73	4.5	9,642	156
% Increase		56%				-6.7%	16%	-6%	25%	31%
	Mechanical efficiency increased more than 37%									

Further consideration of the data obtained from the patients who were restudied is suggestive. In three instances the minute outputs at the height of congestive failure were greater than they were three to six weeks later, when the patients had apparently recovered, although, as previously noted, an immediate increase in stroke volume had been found two hours after the intravenous injection of lanatoside C.

Two of these same patients were available for kymographic studies three and thirteen months after the first control measurements were obtained. Both were fully compensated at this time. In one patient (C. H.) the stroke output was slightly elevated, but, in the other (F. S.), it had decreased approximately to the value obtained before any cardiac glycoside had been given. The diastolic volume, however, was 300 c.c. less than at the time of the control kymogram in both instances (Tables II and IV).

These facts suggest a possible explanation of the inconstancy of results in cardiac output studies before and after the disappearance of congestive heart failure. It may be that significant changes in cardiac output should be looked for during the period of transition between a state of congestive failure and of compensation. In accordance with the backward failure theory, expounded by Harrison,[14] changes in cardiac output of small degree which occur in a relatively short period of time may result in extensive venous congestion. Similarly, relatively small increments in minute volume during a comparatively short time should result in prompt lessening of the symptoms and signs of pulmonary and venous congestion. The fact that the increases in cardiac output which occurred immediately after the administration of lanatoside C were not always permanent is consistent with this impression.

TABLE III

INDIVIDUAL CIRCULATORY MEASUREMENTS BEFORE, AND 3 TO 6 WEEKS AFTER, THE INTRAVENOUS INJECTION OF LANATOSIDE C, WHEN THE PATIENTS HAD BECOME COMPENSATED

TIME	BL.P.	P.P.	H.R.	C.T.	V.P.	D.H.V.	S.O.	M.O.	P.P. × H.R.	WORK/ BEAT
12/21/40	*L. P., Female, Age 68, Hypertensive Heart Disease*									
Control	190/90	100	77	25.9	9	849	63	4.8	7,700	119
1/11/41	210/92	118	62	25.8	6	838	106	6.6	7,316	226
% Increase		11.8%				-1%	68%	39%	-5%	90%
11/29/40	*C. F., Male, Age 61, Hypertensive and Arteriosclerotic Heart Disease*									
Control	120/96	24	96	46	22	973	24	2.3	2,300	35
12/21/40	120/84	36	76	27.3	6	728	41	3.1	2,636	57
% Increase		50%				-25%	73%	35%	15%	63%
2/8/40	*J. H., Male, Age 63, Hypertensive and Arteriosclerotic Heart Disease*									
Control	134/94	40	102	38.2	24	1016	47.6	4.9	4,080	74
3/4/40	152/80	72	88	17.5	6	739	39.2	3.5	6,336	63
% Increase		80%		-54%		-27%	-19%	-28%	55%	-17%
1/30/40	*H. J., Male, Age 69, Arteriosclerotic Heart Disease*									
Control	90/76	14	90	74.3	18	1016	47.6	4.3	1,260	54
3/4/40	90/88	12	88	79.6	10	740	39.2	3.5	1,056	48
% Increase		-14%		6%		-27%	-17%	-18%	-16%	-10%
2/15/40	*A. C., Male, Age 51, Syphilitic Heart Disease, Aortic Insufficiency*									
Control	140/108	32	100	26.2	18	1060	38.2	3.8	3,200	65
3/4/40	158/100	58	78	15.8	8	723	31.7	2.5	4,524	56
% Increase		81%		-40%		-31%	-17%	-34%	41%	-15%
2/13/40	*R. A., Male, Age 46, Syphilitic Heart Disease, Aortic Insufficiency*									
Control	132/60	72	104	35.9	19	1019	38.8	4.0	7,488	50
3/4/40	170/60	110	76	24.5	3.6	738.7	58	4.4	6,840	90
% Increase		48%		-32%		-37%	49%	10%	-8%	80%
1/30/40	*F. S., Male, Age 69, Hypertensive and Arteriosclerotic Heart Disease*									
Control	108/82	26	104	59.2	21	997	37	3.8	2,704	47
3/4/40	160/76	84	76	27.5	5.6	782	75.5	5.74	6,384	121
% Increase		215%		-53%		-21%	140%	50%	136%	150%

TABLE IV

INDIVIDUAL CIRCULATORY MEASUREMENTS FROM 2 PATIENTS BEFORE THE INJECTION OF LANATOSIDE C AND AFTER 3 AND 13 MONTHS

TIME	BL.P.	P.P.	H.R.	C.T.	V.P.	D.H.V.	S.O.	M.O.	P.P. × H.R.	WORK/ BEAT
1/30/40	*F. S., Male, Age 69, Hypertensive and Arteriosclerotic Heart Disease*									
Control	108/ 82	26	104	59.2	21	997	37	3.8	2,704	47
3/1/41	180/110	70	66	23.6	7.0	686	37.3	2.5	4,620	75
% Increase		169%		-58%		-31%	1%	-35%	71%	60%
12/30/40	*C. H., Male, Age 69, Arteriosclerotic Heart Disease*									
Control	132/84	48	96	28	21	1068	66	6.2	4,608	95
3/1/41	158/82	76	90	18.5	6.0	695	79	7.1	6,840	129
% Increase		58%		-34%		-35%	16%	14%	45%	36%

Bl.P.—Blood pressure
P.P.—Pulse pressure
H.R.—Heart rate
C.T.—Circulation time
V.P.—Venous pressure
D.H.V.—Diastolic heart volume
S.O.—Stroke output
M.O.—Minute output
P.P. × H.R.—Pulse pressure times heart rate
Work/beat—Mean blood pressure times stroke output in gram meters

The much smaller diastolic heart volume in our patients after the establishment of compensation is significant, and is in accord with the results of Stewart and his co-workers.[10]

CONCLUSIONS

1. The intravenous administration of lanatoside C to patients with heart failure and normal sinus rhythm usually increases the pulse pressure and reduces the circulation time and venous pressure within two hours. Roentgenkymographic studies of the hearts of ten such patients showed that the drug produced a significant reduction of diastolic heart volume in five patients and an increase in stroke output in eight patients. In two patients, the minute volume of the heart was so large before the administration of the drug that no great increase could be expected.

2. In the eight patients who responded with increased cardiac output, the product of the stroke output and the mean blood pressure was definitely increased, whereas the diastolic heart volume decreased or was unchanged. Since the diastolic heart volume is an index of oxygen consumption, these increases in work which resulted from the administration of lanatoside C must have represented proportional improvement in the mechanical efficiency of the hearts of eight of the ten patients studied.

3. In seven patients who were restudied after the establishment of compensation, there was a decrease of 200 c.c. or more in the diastolic heart volume. In four patients, the minute volume was greater than at the start of the experiment, and in three patients it was less.

4. The most consistent and lasting change in the failing heart that is produced by the administration of lanatoside C seems to be a decrease in its diastolic volume, or oxygen consumption.

We wish to thank Dr. Ancel Keys and his staff for their invaluable assistance in making the planimetric measurements from the teleoroentgenkymograms, in applying the Keys and Friedell formula to the obtained data, and for their generous help in carrying out some of the experiments.

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THROMBOSIS OF THE SUBCLAVIAN AND AXILLARY VEINS

Report of 46 Cases

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THROMBOSIS of the veins of the lower extremity is so frequent as to be a matter of common experience. The same condition in the veins of the upper extremity seems to be so relatively infrequent that a single investigator's experience is limited to a few cases. However, thrombosis of the subclavian and axillary veins is perhaps more common than is generally realized. In point of fact, one of us (J. R. V.) has previously reported[1] 17 such cases, and in the past three years we have observed 29 additional cases. It is our purpose in this report to present the data obtained from the study of all 46 cases.

The clinical manifestations of thrombosis of the subclavian and axillary veins vary, depending on whether the obstruction develops acutely or gradually. In the cases in which the thrombosis begins acutely, pain is usually the initial symptom. The pain begins in the region of the shoulder and extends down the arm to the hand. This generalized pain and the cyanosis and coldness of the finger tips which appear almost simultaneously are the result of vasospasm. Weakness and numbness of the extremity develop, and the weakness may progress until the function of the arm is lost. Within a short time, swelling of the hand and arm becomes apparent and may increase rapidly, so that the affected extremity sometimes reaches twice its normal size within a few hours. The pulse rate is usually normal unless there is some other cause for tachycardia. The systolic blood pressure is often 10 to 15 mm. higher on the affected side than in the normal arm. There are local pain and tenderness over the thrombosed portions of the involved veins. Because of the edema, the superficial veins of the arm are not readily seen, but the antecubital veins usually are palpably distended. The initial pressure in these veins is invariably above normal (usually more than 300 mm. of saline), and rises promptly to a higher level when the patient opens and clenches the fist repeatedly while the venous pressure is being measured.[2] The circulation time from the involved extremity to the lung or tongue is prolonged. The oxygen content of the venous blood is decreased. A venogram will reveal the obstruction, the extent of involvement of the veins, and the developing collateral venous channels.

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After acute thrombosis of the subclavian and axillary veins, the generalized pain in the arm and cyanosis of the digits disappear as soon as vasospasm is released. This usually takes place promptly after beginning appropriate treatment. The relief of edema and weakness depends upon re-establishment of the circulation, and is necessarily a slower process. The rapidity of improvement at this stage varies primarily with the location and extent of the thrombosis, and secondarily, with the number and size of collateral channels.[3] In cases in which only a short segment of the subclavian or axillary vein is involved, collateral venous channels soon begin to function, the venous pressure falls, and the edema disappears within five to seven days. In cases of more extensive involvement, the venous pressure remains elevated because of inadequacy of the collaterals, so that the edema subsides more slowly and tends to recur with exercise. In some cases the edema never disappears completely. In such cases, and in those in which there is an abnormal elevation of local venous pressure with exercise, use of the arm soon results in fatigue or even pain. The postthrombotic stage after acute thrombosis of the subclavian and axillary veins then resembles closely the clinical picture which develops in cases of gradual occlusion of these veins.

Gradual occlusion of the subclavian and axillary veins is almost always secondary to some other disease, usually a malignant neoplasm involving the thorax. In some cases, therefore, the manifestations of the venous obstruction may be overshadowed by the primary disease. The first symptoms of thrombosis which develops gradually are usually slight enlargement and fatigability of the affected arm. The swelling of the arm may be comparatively slight, and pitting edema is not necessarily present. Vigorous or prolonged use of the arm may cause an increase in the swelling or may be impossible because of the fatigue which results from exercise. Collateral veins appear over the upper part of the arm, the shoulder, and the chest, and the veins of the forearm and hand are obviously engorged with blood. The initial venous pressure in the affected arm is higher than normal, but usually below 300 mm. of saline. Exercise of the hand produces a further elevation of the venous pressure.[2] The circulation time from the affected arm to the lung or tongue may be prolonged, but is often within normal limits. As in cases of acute thrombosis, the venogram will reveal the obstruction and the extent of involvement of the veins, and the collateral venous channels will be visualized. In the cases in which gradual occlusion is secondary to a malignant neoplasm, the progress of symptoms in the affected arm is variable. As the neoplasm grows, the thrombosis may spread, with a consequent aggravation of symptoms. In some cases the clinical picture will suddenly change from one of gradual occlusion to one of acute obstruction.

An etiologic classification of cases of thrombosis of the subclavian and axillary veins offers some difficulty. We have listed our cases in

groups which represent the major causative factors (Table I). It must be understood that in some instances more than one factor is important in the pathogenesis of the disease.

TABLE I

CLASSIFICATION OF 46 CASES OF SUBCLAVIAN AND AXILLARY VEIN THROMBOSIS

		CASES
A. Thrombosis complicating heart failure		16
1. Stasis thrombosis	13 cases	
2. Chemical thrombosis	2 cases	
3. Thrombosis secondary to local infection	1 case	
B. Traumatic, or effort, thrombosis		10
C. Thrombosis secondary to neoplasm		18
D. Thrombosis from operative scar		2
		46

THROMBOSIS COMPLICATING HEART FAILURE

Thrombosis of the peripheral veins is a common complication of congestive heart failure. The presence of such thrombosis is often unrecognized because of the prominence of the manifestations of heart failure. Its importance has not been generally emphasized. However, Hampton and Castleman[4] showed that of 370 autopsy cases of pulmonary embolism 30 per cent were cardiac patients. The source of a very large percentage of the emboli in these cases was "symptomless" thrombosis of the deep veins of the legs. This study and White's[5] experience indicate the extreme importance in heart failure of peripheral venous thrombosis as a cause of death from pulmonary embolism, or as a cause of prolongation of the period of heart failure in cases in which pulmonary embolism is not fatal.

Thrombosis of the veins of the upper extremity is quite infrequent as compared with the lower extremity. In a statistical study[6] of 1,260 cases of postoperative venous thrombosis involving 1,401 locations, Barker, et al., found that the veins of the lower extremity were the site of 85.6 per cent of the thromboses, whereas involvement of the veins of the upper extremity constituted only 1.7 per cent of the total. Thrombosis of the veins of the upper extremity in cases of heart failure has rarely been mentioned in the literature. Since 1900, when Welch reviewed the subject[7] and reported several cases that he had personally observed, there has been no important consideration of the condition. However, our experience has led us to believe that it is a more freqent complication than is indicated by the sparsity of reports. In the past five years we have observed 16 cases of subclavian and axillary vein thrombosis complicating heart failure (Table II).

In all of these 16 cases the slowing of the venous circulation that accompanies heart failure was undoubtedly important in predisposing to venous thrombosis, and in 13 of the cases it was the only apparent causative factor. In 2 of the cases "chemical" thrombosis, caused by

TABLE

SUBCLAVIAN AND AXILLARY VEIN THROMBOSIS

CASE	AGE	SEX	RACE	CARDIAC DIAGNOSIS	DURATION OF HEART FAILURE	LOCATION OF THROMBOSIS	ONSET	SYMPTOMS
1	68	M.	B.	Hypertensive heart disease	3 weeks	Left subclavian	Acute	Edema of left arm
2	71	F.	B.	Hypertensive heart disease	1 year	Left subclavian	Acute	Edema, weakness of left arm
3	48	F.	B.	Syphilitic heart disease	7 months	Left subclavian	Acute	Edema, weakness of left arm
4	40	M.	B.	Hypertensive heart disease; dissecting aneurysm	3 months	Left subclavian	Acute	Edema of left arm
5	67	F.	B.	Hypertensive heart disease (cerebral hemorrhage)	Several days?	Left subclavian and axillary veins	Acute	Edema of left arm
6	65	F.	W.	Hypertensive heart disease	7 months	Left subclavian	Acute	Pain in left shoulder and arm; edema
7	29	F.	W.	Rheumatic heart disease	14 months	Right subclavian	Acute	Pain in right arm; edema
8	30	M.	B.	Syphilitic heart disease	1 year	Right basilic, axillary and subclavian	Acute	Pain in right arm after injection of mercupurin; tenderness; edema
9	48	M.	B.	Hypertensive heart disease	2 weeks	Left subclavian and axillary	Acute	Pain in left axilla; edema and weakness of arm
10	33	F.	B.	Hypertensive heart disease	2 months	Left subclavian and axillary	Acute	Pain in left pectoral region and arm; edema of left arm and breast; later prominent collateral veins
11	57	M.	W.	Coronary artery sclerosis	3 weeks	Right basilic, axillary and subclavian	Gradual	Thrombosis followed numerous injections of mercupurin; prominent veins at shoulder; hard thrombosed veins

II

COMPLICATING HEART FAILURE

CIRCULATION TESTS		VENOGRAM	COURSE AND TERMINATION	AUTOPSY
AFFECTED ARM	UNAFFECTED ARM			
V.P. 350 mm.	V.P. 275 mm.		Pulmonary infarction; death	
			Pulmonary infarction? improvement; left hospital	
V.P. 265 mm. C.T. 47 sec.	V.P. 190 mm. C.T. 53 sec.		Pulmonary infarction; improvement; left hospital	
			Pulmonary infarction; dissecting aneurysm; death	Thrombosis of left subclavian vein extending into innominate vein; pulmonary infarction; hypertensive heart disease; dissecting aneurysm
V.P. 335 mm. C.T. 16 sec.	V.P. 110 mm. C.T. 13 sec.		Pulmonary infarction; bronchopneumonia; death	Thrombosis of left subclavian and axillary veins; pulmonary infarction (small); bronchopneumonia; hypertensive heart disease
V.P. 265 mm. V.P.Ex. 360 mm. C.T. 52 sec.	V.P. 235 mm. V.P.Ex. 250 mm. C.T. 40 sec.	Confirmatory	Gradual improvement; left hospital	
		Confirmatory	Intractable heart failure; death	Thrombosis of right subclavian vein extending into internal jugular and innominate veins; multiple pulmonary infarcts; rheumatic heart disease
V.P. 365 mm. V.P.Ex. 390 mm.	V.P. 265 mm. V.P.Ex. 260 mm.	Confirmatory	Death from pulmonary embolism	
V.P. 295 mm. V.P.Ex. 350 mm. C.T. 47 sec.	V.P. 290 mm. V.P.Ex. 290 mm. C.T. 36 sec.		Pulmonary infarction; death	Thrombosis of left subclavian and axillary veins; small pulmonary infarcts; hypertensive heart disease
V.P. 240 mm. V.P.Ex. 390 mm. C.T. Blank	V.P. 115 mm. V.P.Ex. 150 mm. C.T. 11 sec.	Confirmatory	Long course; repeated pulmonary infarction; later thrombosis of left femoral and iliac veins; death	Hypertensive heart disease; cardiac mural thrombi; old thrombosis left innominate, internal jugular, subclavian and axillary vv.; recent thrombosis left iliac and femoral vv.; multiple pulmonary infarcts
		Confirmatory	Improvement; left hospital	

TABLE

CASE	AGE	SEX	RACE	CARDIAC DIAGNOSIS	DURATION OF HEART FAILURE	LOCATION OF THROMBOSIS	ONSET	SYMPTOMS
12	26	F.	B.	Rheumatic heart disease	3 months	Left subclavian, axillary, brachial, and external jugular	Acute	Thrombophlebitis following furuncle over external jugular vein; pain, edema of left arm
13	66	F.	W.	Hypertensive heart disease		Left subclavian and axillary	Acute	Pain, weakness, edema of left shoulder and arm; later collateral veins
14	55	F.	B.	Hypertensive heart disease	Several months	Left subclavian and axillary	Acute	Pain in neck and arm; edema; later prominent collateral veins
15		F.	B.	Hypertensive heart disease	Several days	Left subclavian and axillary	Acute	Pain, edema, coldness of left arm
16		F.	W.	Hypertensive heart disease	Several weeks	Right subclavian and axillary	Acute	Pain, edema, coldness of right arm

V.P. = Venous pressure.
V.P.Ex. = Venous pressure after exercise of hand for one minute.
C.T. = Arm-to-tongue circulation time.

intravenous injections of a mercurial diuretic, extended to the auxillary and subclavian veins from the veins of the arm. In one case the thrombosis apparently resulted from spread of infection from a furuncle which lay over the external jugular vein. The cause of the heart disease is apparently not important in the incidence of subclavian and axillary vein thrombosis. Most of our cases were in patients with hypertensive heart disease, but this is to be explained by the greater frequency of this type in the hospitals in which our studies were made. On the other hand, the severity of the heart failure seems to be important in the causation of the venous thrombosis. In all but 2 of the 16 cases, the heart failure was so severe that the patients were bedridden. It is interesting that in 12 cases the veins of the left arm were involved, and in 4 cases, the veins of the right arm. One apparent reason for this disparity of incidence is the longer, more devious course taken by the left innominate vein. Another possible reason is that the patient who is bedridden makes greater use of the right arm than of the left. This incidence is in contrast to that in cases of traumatic thrombosis, in which the veins of the right arm are usually affected.[1]

In 15 of the 16 cases the onset of symptoms was acute. In the one case in which the onset was gradual, thrombosis developed after repeated injections of a mercurial diuretic, and there were no outstanding symptoms except prominent collateral veins and hardness of the basilic and axillary veins. In most of the cases in which there was an acute onset, the first symptom was pain in the arm or region of the shoulder. All of the patients rapidly developed edema, usually of severe degree. The significance of edema of one arm in a case of severe heart failure probably is not always immediately appreciated because

II—Cont'd

CIRCULATION TESTS		VENOGRAM	COURSE AND TERMINATION	AUTOPSY
AFFECTED ARM	UNAFFECTED ARM			
		Confirmatory	Gradual improvement; left hospital	
		Confirmatory	Gradual improvement; left hospital	
		Confirmatory	Gradual improvement; left hospital	
		Confirmatory	Gradual improvement; left hospital	
		Confirmatory	Death from heart failure	

of the prominence of the symptoms of heart disease. For this reason, thrombosis of the subclavian and axillary veins may be overlooked. Four patients complained of weakness of the affected arm. It is to be remembered that all of the patients were severely prostrated, so that weakness of one arm was probably not readily noticed. In all cases in which the venous pressure was measured, it was found to be abnormally high on the affected side, ranging from 240 to 365 mm. of saline. In the unaffected arm also the venous pressure frequently was elevated because of heart failure, but usually not to the same extent as on the side of the thrombosis. In all cases in which the "exercise test" was used, there was a prompt and substantial increment in the venous pressure on the affected side, but on the nonobstructed side there was little or no change. For this reason, the "exercise test" has proved to be of particular value in the diagnosis of peripheral venous obstruction complicating congestive heart failure. The circulation time measurements were of little value in confirming the presence of the venous thrombosis.

The course of subclavian and axillary vein thrombosis in cases of heart failure may tend slowly toward recovery, but is commonly interrupted by grave complications. Propagation of the thrombus is favored by the generalized slowing of the venous circulation and by the patient's inactivity. Under these circumstances it is not surprising that embolism is a frequent occurrence. In 9 of the 16 cases in this series, pulmonary embolism occurred, and in 7 it was fatal. In 4 of the 5 autopsy cases the only source that was disclosed for the pulmonary embolism was the thrombus in the subclavian and axillary veins. In the other case there were other sites of thrombosis, any of which may have been the origin of the pulmonary embolism. In the two cases in which the patients died but were not autopsied, the only apparent

source for the pulmonary emboli was in the thrombosed veins of the arm. In the two cases of pulmonary embolism that did not end fatally, there seemed to be considerable aggravation and prolongation of the heart failure as a result of the embolism.

TRAUMATIC, OR EFFORT, THROMBOSIS

The exact pathogenesis of this type of thrombosis remains obscure. In a previous communication one of us reviewed the various theories,[1] and since that time nothing of importance has been added to the knowledge of the subject. Thrombosis may result from a variety of incidents, some trivial, some severe. In some cases there is no obvious preceding effort or trauma. In 8 of the 10 cases which we have classified as traumatic, or effort, thrombosis of the subclavian and axillary veins, the exciting causes include direct contusion of the shoulder region (3 cases), carrying a heavy weight by hand, a fall on the outstretched hand (Fig. 1), working with the arms overhead, washing clothes by hand, and sleeping with the arm outstretched under the head. In the remaining 2 cases there was no definite history of any unusual effort or of direct trauma.

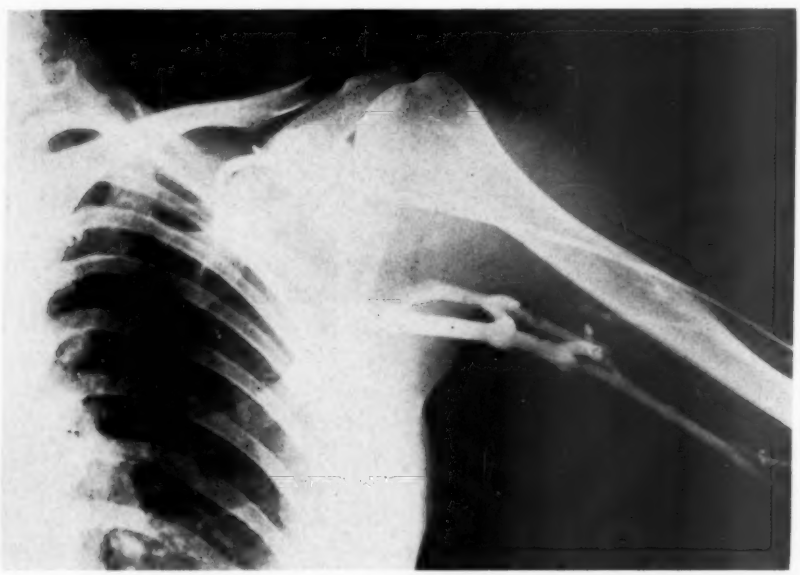

Fig. 1.—Venogram demonstrating acute occlusion of subclavian vein caused by fall on outstretched hand.

Traumatic thrombosis of the veins of the upper extremity is not of frequent occurrence. This can best be judged by the fact that the majority of reports on the subject deal with one or a few cases. The onset of symptoms of this type of thrombosis is acute, and the manifestations and course closely follow the description of acute thrombosis,

as given above. The thrombosis which follows effort almost always occurs on the right side in right-handed persons, and that which follows trauma occurs, of course, on the side that is injured.

Embolism practically never results from this type of thrombosis. This is in direct contrast to the experience with thrombosis which complicates heart failure, and is probably to be explained by the fact that in traumatic, or effort, thrombosis there is no general venous stasis, and the patient usually is not bedridden and uses his arm more actively, so that treatment is effective in limiting propagation of the thrombus.

It should be emphasized that, although collateral circulation usually develops sufficiently to relieve the acute symptoms, there is almost invariably some residual impairment of the circulation. This can be demonstrated objectively by measuring the venous pressure on the affected side during exercise of the hand. In such cases the patient finds that his arm tires quickly or may even become painful during exercise. In some cases edema may reappear after prolonged exertion. Fig. 2 is an example of persistence of postthrombotic manifestions.

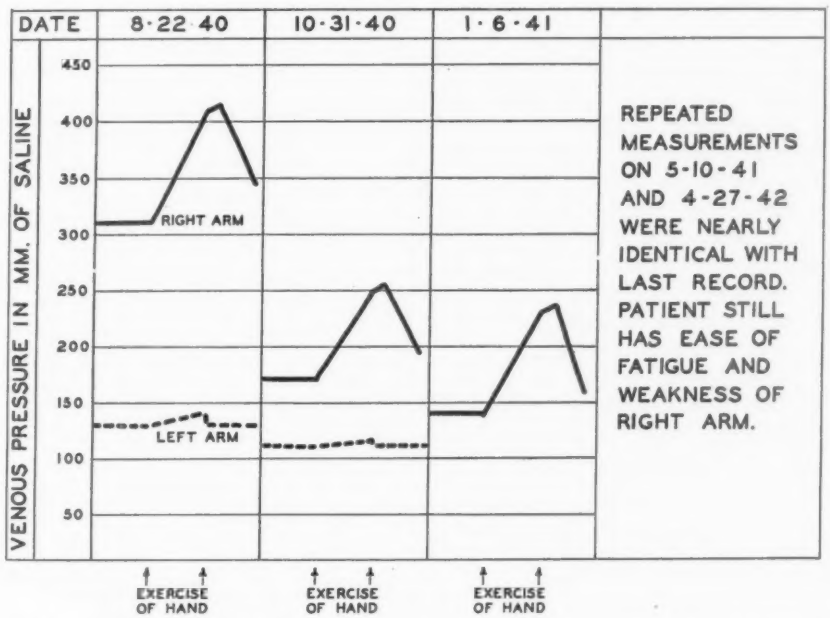

Fig. 2.—Right subclavian and axillary vein thrombosis (traumatic). Onset 8/19/40.

THROMBOSIS SECONDARY TO NEOPLASM

The most common cause of thrombosis of the subclavian and axillary veins is a malignant neoplasm of the chest or axilla. Eighteen of the 46 cases in our series fell in this group. The most common neoplasm was carcinoma of the breast, of which there were 9 cases. This number

is probably smaller than would be expected during five years of experience at a large general hospital, but we have included only cases which we have personally observed. Nor have we included in this report a consideration of the type of axillary vein obstruction which frequently follows the alteration of the course of the axillary vein[8] produced by radical mastectomy. The other types of neoplasm were as follows: bronchiogenic carcinoma, 6 cases; lymphosarcoma, 1 case; sarcoma of the prostate, 1 case; and sarcoma of the ovary, 1 case.

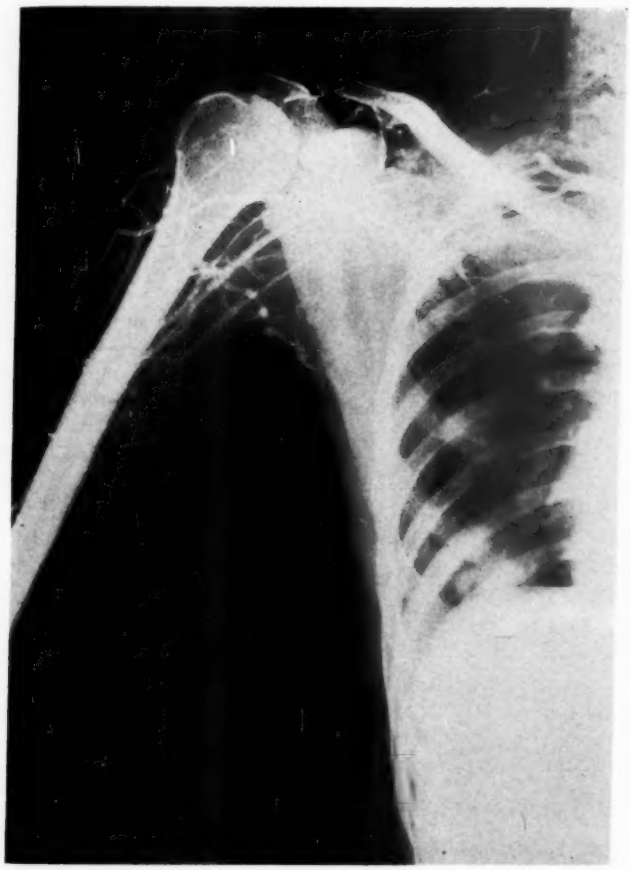

Fig. 3A.—Venogram showing occlusion of subclavian, axillary, and basilic veins secondary to metastasis from sarcoma of the prostate. Note numerous small collateral vessels.

It has long been recognized that malignant neoplasms exert an unexplained influence on the coagulation of the blood, so that there is an increased tendency to peripheral venous thrombosis. This may develop without apparent reason at a point distant from the site of the neoplasm. However, we have not observed an instance of subclavian and axillary venous thrombosis secondary to neoplasm in which there was

not an adequate mechanical and anatomic explanation for the involvement of the vein. There may be a direct invasion of the vein by the neoplasm, with obstruction primarily as the result of a filling of the lumen of the vein by the malignant growth. In other cases only the wall of the vein is invaded, and thrombosis follows. In still other cases the malignant lesion is contiguous to the vein, but does not invade it. In this last type of case, thrombosis results from compression or distortion of the vein.

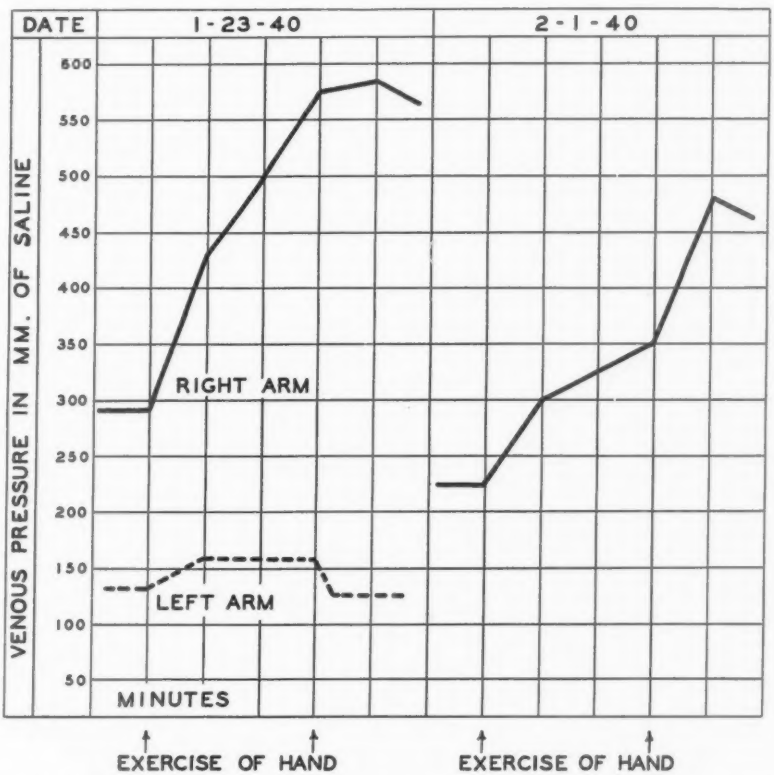

Fig. 3*B*.—Same case as Fig. 3*A*, showing difference in venous pressure measurements in the arms. Note the persistent elevation of venous pressure in the affected arm. Right subclavian and axillary vein thrombosis (neoplastic).

In most of the cases of this type of thrombosis, the first symptom noticed by the patient is swelling of the arm, so that the onset seems to be acute. However, in cases in which there has been an opportunity to observe the patient prior to the time of development of acute symptoms, there are often evidences of gradual occlusion of the subclavian and axillary veins. In some there are quite obvious collateral veins at the shoulder region long before the patient is aware of any trouble with the arm. Therefore, although the patient may not seek medical aid until there are acute symptoms, it is probable that in many cases the venous obstruction has been a slowly developing process (Fig. 3*A*

and *B*). Of the common types of subclavian and axillary vein thrombosis, that which is secondary to neoplasm is the only one in which the onset of symptoms is usually gradual.

The symptoms of thrombosis secondary to neoplasm differ somewhat from the classical descriptions of acute thrombosis. In the first place, the pain which results from vasospasm in the other types of thrombosis may be entirely absent. However, there is often another type of pain in the shoulder, neck, and arm. This pain is caused by involvement of the brachial plexus by the malignant neoplasm. It is persistent, peculiarly severe, and progressive. Paralysis of the arm may eventually follow such involvement of the brachial plexus. In the second place, the edema which characterizes complete obstruction of the veins shows less tendency to recede, and, indeed, usually becomes progressively more severe. These patients are then subject to recurrent attacks of lymphangitis, lymphadenitis, and cellulitis, such as those which accompany the postthrombotic syndrome in the lower extremity. In the third place, as mentioned in the discussion of the onset, there may be obvious collateral veins before the edema appears. If the patient is not seen until edema has developed, the presence of prominent collateral veins is strong presumptive evidence that a neoplasm has caused the thrombosis.

The course of this type of thrombosis is governed by the progress of the underlying disease, which eventually terminates fatally. As far as we have been able to observe, pulmonary embolism has not resulted from this type of thrombosis. However, pulmonary involvement by the neoplasm, which was present frequently in these cases, may possibly have prevented the recognition of symptoms of pulmonary embolism.

THROMBOSIS FROM POSTOPERATIVE SCARRING

Occasionally, after radical removal of the breast,[8] thrombosis of the axillary and subclavian veins results from gradual obstruction of the axillary vein by scar tissue. The axillary vein may be obstructed by simple constriction by scar tissue, without actual thrombosis. In other cases, the vein is occluded when the patient's arm hangs down beside the chest wall. This is the result of the alteration in the course of the vein which follows removal of the pectoral muscles. Cases of obstruction of the axillary vein without thrombosis have not been considered in this report. However, in this series of 46 cases, there were 2 in which thrombosis of the axillary vein followed constriction by scar tissue. These cases are described briefly.

CASE REPORTS

M. J., a 66-year-old Negress, was first seen by us in 1939. Three years prior to that time a radical mastectomy had been performed for carcinoma of the left breast. About 10 weeks after the operation, following deep roentgen therapy to the axilla and chest, the patient developed pain along the inner aspect of the left

arm and in the axilla. The entire left upper extremity became swollen. This swelling remained, although it tended to subside somewhat after a period of rest. On examination, the affected arm was obviously enlarged, and there was pitting edema. The veins in the antecubital fossa were large and distended. Other veins in the forearm and hand were obscured by edema. The initial venous pressure in the left antecubital vein was 160 mm. of saline. The pressure rose rapidly and astonishingly, with exercise of the hand, reaching 820 mm. after three minutes (Fig. 4). A venogram showed complete obstruction of the left axillary vein. The patient was seen frequently in the Surgical Outpatient Clinic during the next five months. The swelling of the arm persisted. A repetition of the venous pressure measurement at the end of that time gave an initial reading of 130 mm. After exercise of the hand for one minute, the pressure had risen to 960 mm. Early in 1940 the left axilla was explored, and the axillary vein was found to be incarcerated in dense scar tissue. It was completely occluded by an organized thrombus. The scar tissue was excised as completely as possible, and care was taken not to injure any of the collateral veins. After this operation the swelling of the arm became less severe. When the patient was last seen, in 1942, there was only slight swelling of the left arm. However, after prolonged exercise, the edema recurs.

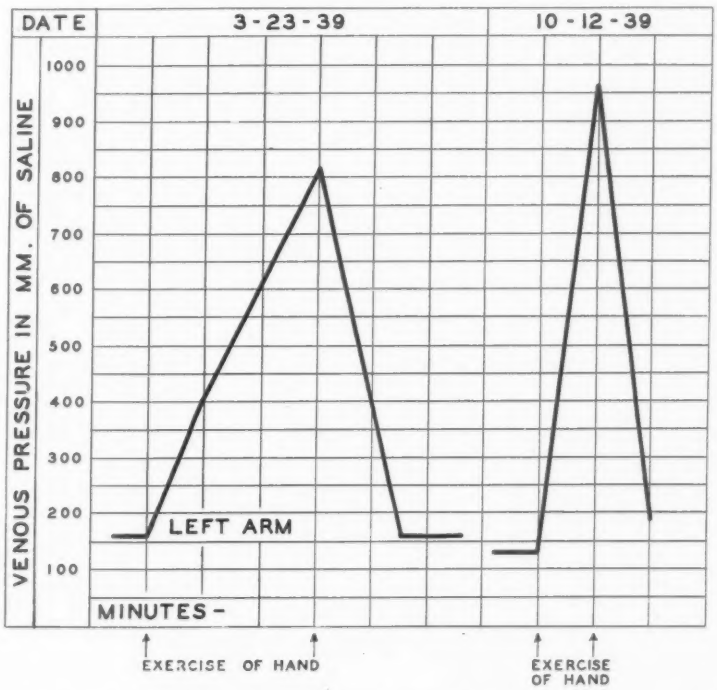

Fig. 4.—Thrombosis of left axillary vein due to constriction by scar of radical mastectomy.

In this case the initial reading of the venous pressure was within normal limits. It was not until the "exercise test" was performed that evidence was obtained that severe venous obstruction was the cause of the edema. Usually, in cases of chronic obstruction of large veins resulting from compression by scar tissue, attempts to relieve the obstruction by means of operation are unsuccessful. However, in this case, there was definite improvement after excision of the scar. Since the axillary vein was occluded by an organized thrombus, the improvement must be attributed to the development of a more adequate collateral circulation.

H. McI., a 68-year-old white woman, was treated in 1932 for carcinoma of the right breast by radical mastectomy and deep roentgen therapy. At an indefinite time after this, the patient noted that the right arm was persistently swollen to a slight degree. By that time, a firmly contracted scar had formed in the right axilla. On several occasions from 1937 to 1942, the right arm became more than usually swollen for a few days at a time, but the patient was not able to ascribe this to any particular activity. In April, 1942, after strenuous use of the right arm and a minor injury to the right elbow, the arm suddenly became painful, tender, and severely swollen. Blotchy areas of redness appeared on the skin, and there was moderate fever. The picture was that of acute lymphangitis and cellulitis superimposed upon chronic venous obstruction. In accordance with our experience in cases of a similar type, in the post-thrombotic syndrome involving the lower extremity,[3] the condition was treated by rest in bed, with the arm abducted and elevated on pillows, the application of warm, moist compresses to the arm, and the administration of sulfadiazine. With this treatment, the patient's fever promptly subsided, and, within a few days, the arm resumed its usual appearance. At that time the initial venous pressure was 170 mm. in the right antecubital vein, and 130 mm. in the left. With exercise of the hand for 1 minute, the venous pressure rose to 190 mm. in the right arm, but remained at 130 mm. in the left.

This case is of interest mainly because it demonstrates that the post-thrombotic syndrome involving the upper extremity may be complicated by lymphangitis and cellulitis similar to that which occurs so commonly in cases of chronic obstruction of the deep veins of the lower extremity. The diagnosis of axillary vein thrombosis in this case has not been confirmed by exploration of the axilla, nor has a venogram been made.

SUGGESTIONS ON TREATMENT

During the acute phase of thrombosis of the subclavian and axillary veins, the arm should be elevated, and warm, moist compresses applied. Active movement of the hand should be encouraged. The position of the arm should be changed from time to time in order to prevent fatigue and joint pain. As suggested by Ochsner and DeBakey,[9] temporary cervicodorsal sympathetic block is helpful in those cases in which there is evident vasospasm. As the symptoms subside, the compresses are discontinued and more active use of the arm is permitted.

Because of the frequency of pulmonary embolism in cases of subclavian and axillary vein thrombosis complicating heart failure, it is suggested that the subclavian vein be ligated proximal to the thrombus. Such an operation is feasible because the subclavian vein can be readily exposed at the base of the neck, under local anesthesia.

When the acute phase has subsided, little or no treatment is necessary. In cases in which there is considerable residual obstruction, the patient may find it necessary to limit the use of his arm in order to avoid fatigue, pain, or recurrence of edema.

SUMMARY AND CONCLUSIONS

Thrombosis of the subclavian and axillary veins is probably more common than is generally realized. This report is based on 46 cases which we have observed during the past five years. In sixteen cases the thrombosis occurred as a complication of heart failure, in 10 it

was the result of effort or trauma, in 18 it was secondary to neoplasm, and in 2 it resulted from scar formation in the axilla.

A discussion of the general symptomatology is given, and variations peculiar to each of the main etiologic groups have been pointed out. The importance of measuring the venous pressure locally during exercise of the hand, as well as at rest, has been emphasized. The value of venograms in confirming the diagnosis and ascertaining the location of the venous obstruction and the extent of collateral circulation has been indicated.

Because of the high incidence of pulmonary embolism when the thrombosis complicates heart failure, it has been suggested that ligation of the subclavian vein be resorted to in these cases, in addition to the usual palliative measures.

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DISCUSSION

Dr. B. Jablons, Brooklyn, N. Y.—I should like to ask Dr. Veal whether there was any evidence in his cases of reflex involvement of the arterial system; in other words, whether there was spasm of the peripheral arteries.

Dr. J. Murray Steele, New York, N. Y.—It seems to me that this is an extraordinarily interesting phenomenon—the rise of pressure with exercise—and it explains very well something I saw three or four years ago. I did not know anything about this test at that time. While doing a venous pressure measurement, the patient felt a cramp in her arm and began to wiggle her hand. The water rose halfway to the top of the manometer, and now I know why.

I should like to make one other remark. Ten years ago a young boy was given arsphenamine without previously neutralizing the solution and he had an extensive thrombosis of the right axillary, subclavian, and brachial veins. He suffered numerous, successive pulmonary infarcts. Dr. Veal said he had not seen infection in any of the traumatic cases, but this one was extraordinary. There followed a series of seven or eight infarcts.

DR. IRVING S. WRIGHT, New York, N. Y.—There are two additional points which I believe are quite interesting. One was emphasized by Dr. Matas. It has a slightly different turn than that which Dr. Veal emphasized, not that he was in error, but there is an additional aspect. Dr. Veal emphasized the prolonged disability in these cases, and that is correct. But there is another factor which may mislead a man who is not experienced in taking care of axillary venous thrombosis.

Some of the patients with traumatic thrombosis apparently do recover entirely, but, in our experience, if they are allowed to go back to the same work or anything like the same work, involving the same type of motion, they may have a relapse.

Secondly, the question comes up as to the nature of a chemical thrombophlebitis. We have studied some of these cases, and, in a good many instances, it seemed to us that more than the chemical irritation of the solution was involved. In a number of instances, the needle actually penetrated the opposite wall of the vein, so that a small portion of the chemical substance was injected, not only into the lumen of the vein, but also into the wall of the vein, and therefore trauma was partially responsible for setting up an inflammatory process in the wall of the vein. This can be minimized by being certain that the needle is freely movable in the lumen of the vein before injecting.

I noticed from Dr. Veal's roentgenograms that, in at least one of the cases of chemical thrombosis, the vein was blocked all the way up, and not just at the subclavian, which would be additional evidence, in that case at least, that the thrombosing process extended from the site of the needle puncture into the subclavian.

DR. GEZA DE TAKATS, Chicago, Ill.—Will Dr. Veal discuss the treatment of this disease?

DR. A. WILBUR DURYEE, New York, N. Y.—I should like to ask Dr. Veal whether he thinks that, in any of these cases, the thrombosis was caused by pressure of the scalenus muscle.

I believe that, in certain instances, there may be actual mechanical obstruction of the subclavian by the scalenus. In these cases it seems logical, especially after the acute attack subsides, to do a scalenectomy to prevent further recurrence.

I should also like to ask Dr. Veal whether he uses heparin or any other anticoagulant in cases of this kind.

DR. J. ROSS VEAL, Washington, D. C.—As to the question of Dr. Jablons, with regard to reflex arterial spasm, you may have noticed on the first slide that there was a note concerning cyanosis of the finger tips in the cold extremity. We feel that early in the stage of acute thrombosis there is reflex arterial spasm of the entire extremity. This, however, promptly disappears with proper treatment. Later, in the post-thrombophlebitic stage, we have not been able to demonstrate any real spasm or any other effect on the arterial system.

I think we would classify Dr. Steele's case of thrombosis after arsphenamine as one of chemical thrombosis, not mechanical. I was much interested to hear that pulmonary emboli do occur in these cases.

As to Dr. Wright's remarks about when the patient should be discharged after an attack of traumatic thrombosis, our experience has shown that we should not discharge a patient as cured unless his venous pressure has returned to normal limits on exercise. Very often a patient will come and say, "I am all well," and the swelling has disappeared, but, if he tries to go back to work, he will find that he is not able to do his work. And, once you discharge the patient, you put him in a bad position if he is not able to continue his work.

Also, in answer to Dr. Wright, I might say that, in the two cases of chemical thrombosis, the thrombosis seemed to begin at the point of the needle and extend all the way up to the subclavian.

Dr. de Takats has asked about the treatment of traumatic thrombosis. We simply prescribe rest, elevation of the arm, and application of heat. Dr. Ochsner, of New Orleans, has told me that he has used cervicodorsal sympathetic block with novocain, with prompt alleviation of the symptoms. However, we have not used that in our series of cases. We simply put the patient to bed, elevate the arm on pillows, and apply heat. We do allow these patients to move the wrist and elbow. We do not put them at complete rest.

Dr. Duryee's remarks about the scalenus are very important. The scalenus has not been investigated in these cases, and it might have some bearing on the etiology.

As to heparin, I have not had any experience with this drug in these cases of thrombosis of axillary and subclavian veins.

THE ELECTROCARDIOGRAM IN THE HYPERVENTILATION SYNDROME

WILLIAM PAUL THOMPSON, M.D., LOS ANGELES, CALIF.

HYPERVENTILATION is common in patients with anxiety neuroses. The symptoms produced by the unconscious act of overbreathing have recently been emphasized by Kerr, et al.,[1, 2, 3] and by Soley and Shock,[4] and include such common complaints and signs as weakness, dizziness, faintness, fainting, numbness and tingling about the mouth and in the hands and arms, palpitation, tachycardia, sighing respiration, muscular rigidity and cramps, hyperreflexia, tremulousness, and, in advanced cases, fully developed tetany, with carpopedal spasm and a positive Chvostek sign. That patients with the syndrome may have severe precordial pain with radiation to the arms, often suggesting the possibility of coronary artery occlusion, is well illustrated in the cases with which this report is concerned. That marked electrocardiographic abnormalities may also be produced, sometimes of a kind and degree suggestive of myocardial infarction, and much more marked than the simple depression of T previously described,[5, 6, 7, 8] makes recognition of the syndrome of double importance.

That tetany may be produced in healthy persons by overventilation of the lungs has long been known. Kerr, et al.,[1, 2, 3] have directed attention to the ease with which the hyperventilation test may be carried out, and the bizarre and often baffling complaints of patients when the syndrome has been reproduced to the satisfaction of both doctor and patient. We have applied the test to our patients and have been able to reproduce not only the symptoms but the electrocardiographic abnormalities as well.

MATERIAL AND METHOD

Twenty-five patients with the hyperventilation syndrome were observed during the past year at the Los Angeles County Hospital and in private practice.* These patients and a group of healthy hospital interns and resident physicians were studied. In an effort to reproduce the symptoms and electrocardiographic abnormalities, a hyperventilation test was applied in a number of instances to persons who were lying quietly and supine in bed. Forced overbreathing of room air as rapidly as possible and to the greatest extent to which the subject was capable

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was carried out for 90 seconds or until symptoms were produced. In the healthy subjects, it was sometimes necessary to continue the hyperventilation for three minutes in order to produce tetany. Electrocardiograms were taken before and immediately after the breathing and at frequent intervals thereafter until symptoms had disappeared and the electrocardiogram had returned to its original form.

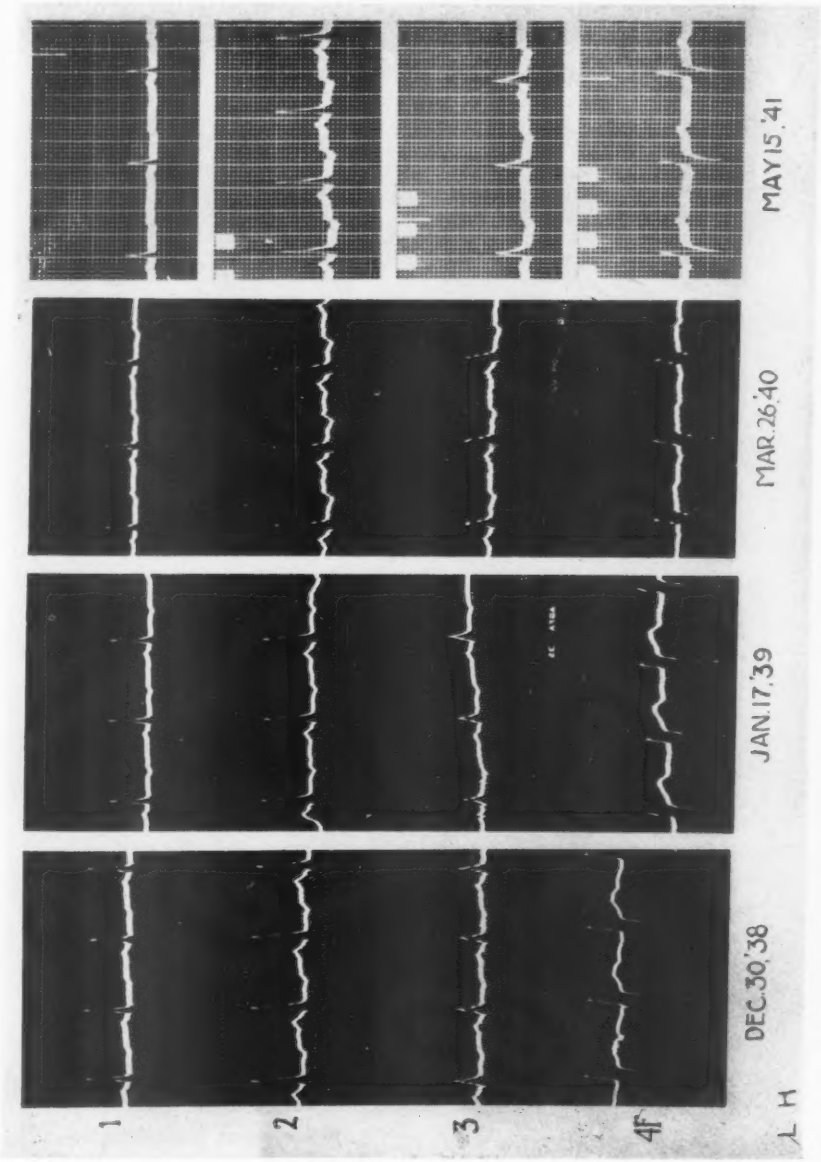

Fig. 1.—Case 1. Hyperventilation syndrome and normal heart. Electrocardiograms taken during the two and one-half years of frequent symptoms.

In a number of instances the carbon dioxide combining power and pH of the venous blood were measured, using a modified Van Slyke bicarbonate titration method and the Beckman pH meter. Hyperventilation with a mixture of 5 per cent carbon dioxide and 95 per cent oxygen was carried out in one normal subject.

The influence on the electrocardiogram of the increase in cardiac rate induced by the hyperventilation exercise was studied subsequently in a few resting subjects after inhalation of amyl nitrite or the intravenous injection of atropine sulphate.

OBSERVATIONS

On Patients with Normal Hearts and the Hyperventilation Syndrome.—Our attention was first directed to the hyperventilation syndrome as a cause of marked electrocardiographic abnormalities by Case

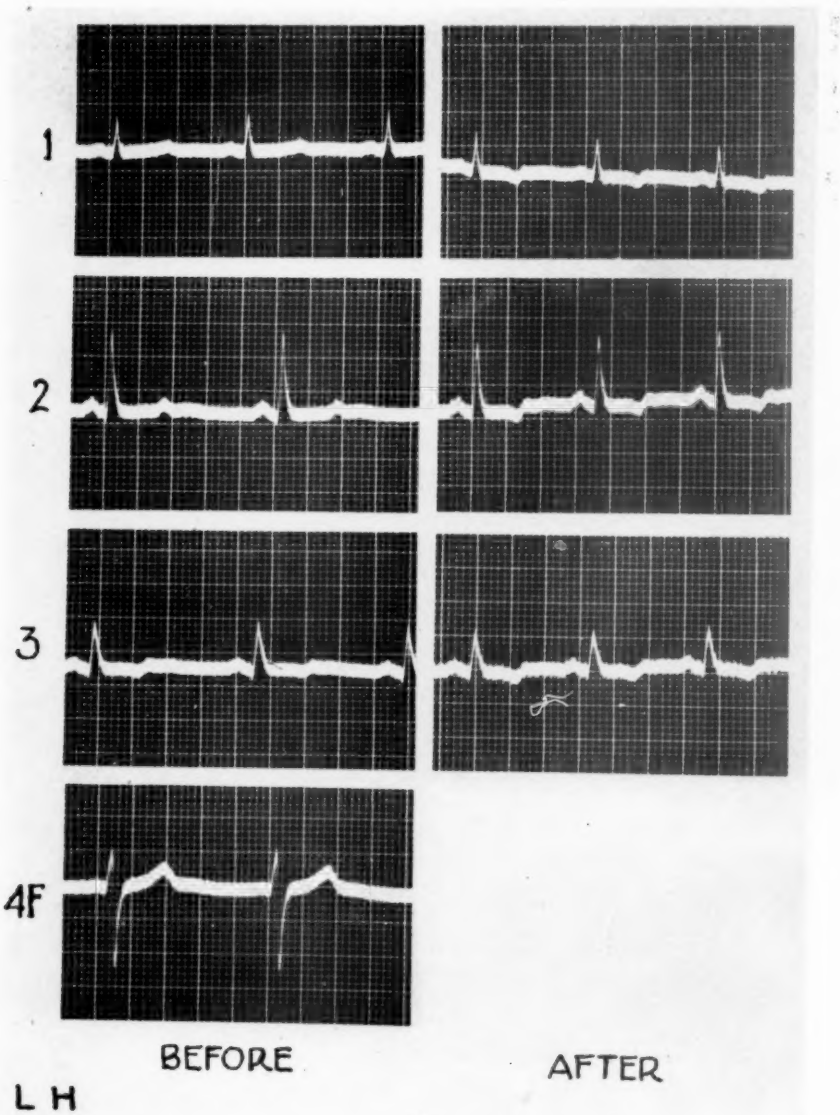

Fig. 2.—Case 1. Hyperventilation syndrome and normal heart. Patient at ease and free of symptoms. Electrocardiograms made before and after forced voluntary hyperventilation for 75 seconds. The T-wave inversion shown in Fig. 1 is reproduced.

1, that of a patient who was long considered elsewhere to have coronary artery occlusion and myocardial infarction. His series of electrocardiograms is reproduced in Fig. 1, and those taken immediately before and after the hyperventilation test are shown in Fig. 2.

CASE 1.—L. H., a man, aged 34 years, was an electric lineman. Two and one-half years before we saw this man he sustained an electric shock which burned his finger and caused momentary difficulty in getting away from the wire. He was weak thereafter but finished the day's work. The next three days he had soreness over the anterior part of the chest, and one month later had the first of a long series of attacks consisting of difficulty in breathing, dizziness, black vision, extreme faintness, weakness, palpitation, tremulousness, and pain across the chest. He thought he had heart trouble, but doctors told him he was nervous. Finally he was hospitalized for study. All tests were negative until "finally an electrocardiogram was taken, and they found out what the trouble was." A diagnosis of coronary occlusion and myocardial infarction was made; he was instructed to rest a great deal, and was finally given work as a bill collector. He disliked his new work intensely. The symptoms became worse, he was forced to be idle much of the time, and spent several long periods in hospitals.

Examination revealed much nervousness at first, but he was at ease later. The hands were cold and clammy. The heart was normal. The blood pressure was 128/86. The lungs were normal. The liver was not enlarged, and there was no edema. A slight, coarse tremor was present in the hands, and the tendon reflexes were moderately hyperactive.

Electrocardiograms taken over a period of two and one-half years were submitted, and are reproduced in Fig. 1. He stated that he had always been frightened while the tracings were being made. His new electrocardiogram, taken while he was entirely at ease, is shown in the left hand column of Fig. 2.

A *hyperventilation test*, consisting of forced overbreathing for seventy-five seconds, reproduced the symptoms of which he complained and the electrocardiographic abnormalities (Fig. 2). Symptoms produced by the test included precordial pain, dizziness, faintness, weakness, numbness, tingling, and tremulousness. A later hyperventilation test, when he was free of symptoms and the CO_2 combining power was 54 volumes per cent, again reproduced the symptoms and electrocardiographic abnormalities. The blood pH changed from 7.36 to 7.43.

The second case is notable with respect to the severity of the symptoms and the extreme inversion of the T waves in all leads (Fig. 3). Since the anxiety neurosis was firmly imbedded in this man, great difficulty was experienced in finding an opportunity to study him while he was free of symptoms and his electrocardiogram was relatively normal. Because his mornings were his best time, repeated visits were made early, with the result shown in the control in Fig. 4. The hyperventilation test reproduced his symptoms with great severity, and the electrocardiographic changes in part. During recovery the result of overcompensation is seen, with T waves taller than in the control.

CASE 2.—W. A. G., a man, aged 51 years, was a carpenter. (L.A.C.H. PF 746-616). For six months he had had almost daily attacks of severe burning, tearing, racking pain across the anterior part of the chest, radiating to the arms, neck, and back, together with great respiratory distress, orthopnea, dizziness, spots before the

eyes, cold sweat, nausea, fear, numbness and tingling, palpitation, and tremulousness. He had been hospitalized elsewhere for most of the six months and had been given much morphine. It was recorded in his progress notes that "the incidence of coronary occlusion in this patient seems to be increasing."

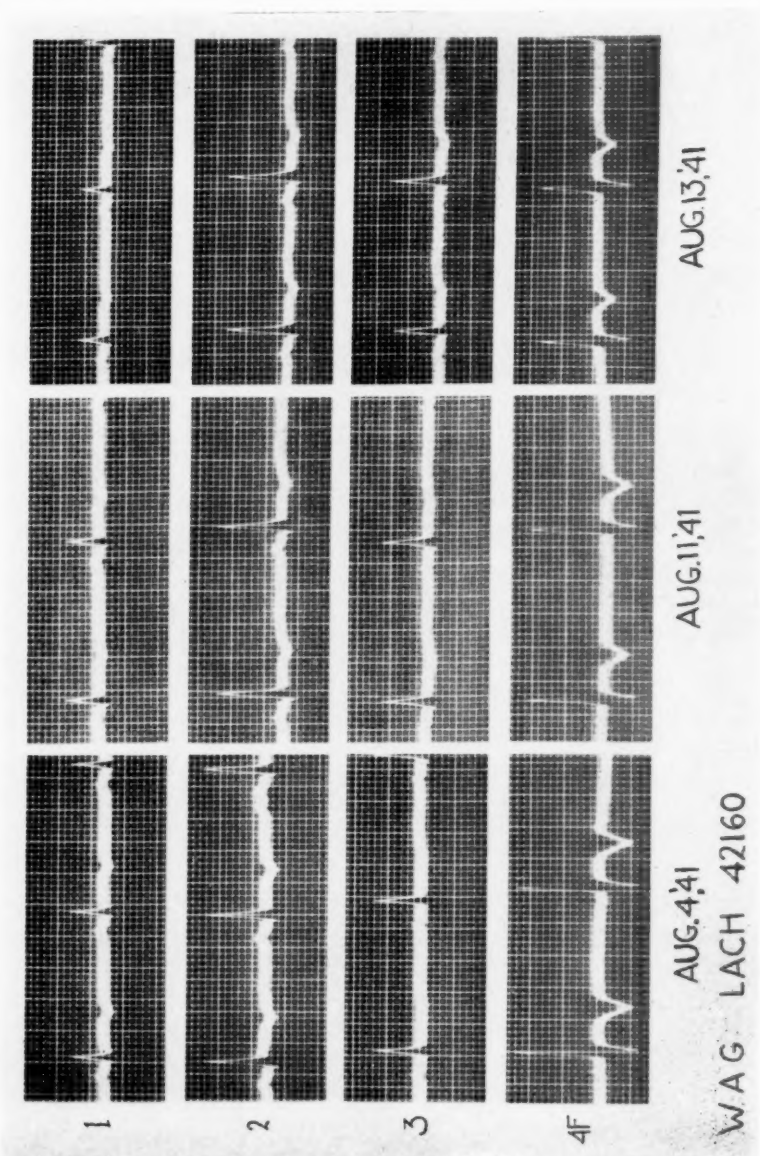

Fig. 3.—Case 2. Hyperventilation syndrome and normal heart. Electrocardiograms taken during period of frequent and severe symptoms.

Examination revealed frequent sighing respiration. Otherwise there was nothing abnormal. The heart was normal. The blood pressure was 106/62. No congestion of the lungs, veins, or liver was present.

Laboratory Data.—The hemoglobin was 110 per cent, the erythrocyte count, 5,560,000, and the leucocyte count, 7,300, with 76 per cent polymorphonuclear neutro-

philes. The corrected sedimentation rate (Wintrobe) was 36 and 19 mm. in one hour on two occasions (maximum normal, 9 mm.). The carbon dioxide combining power and blood pH were not measured.

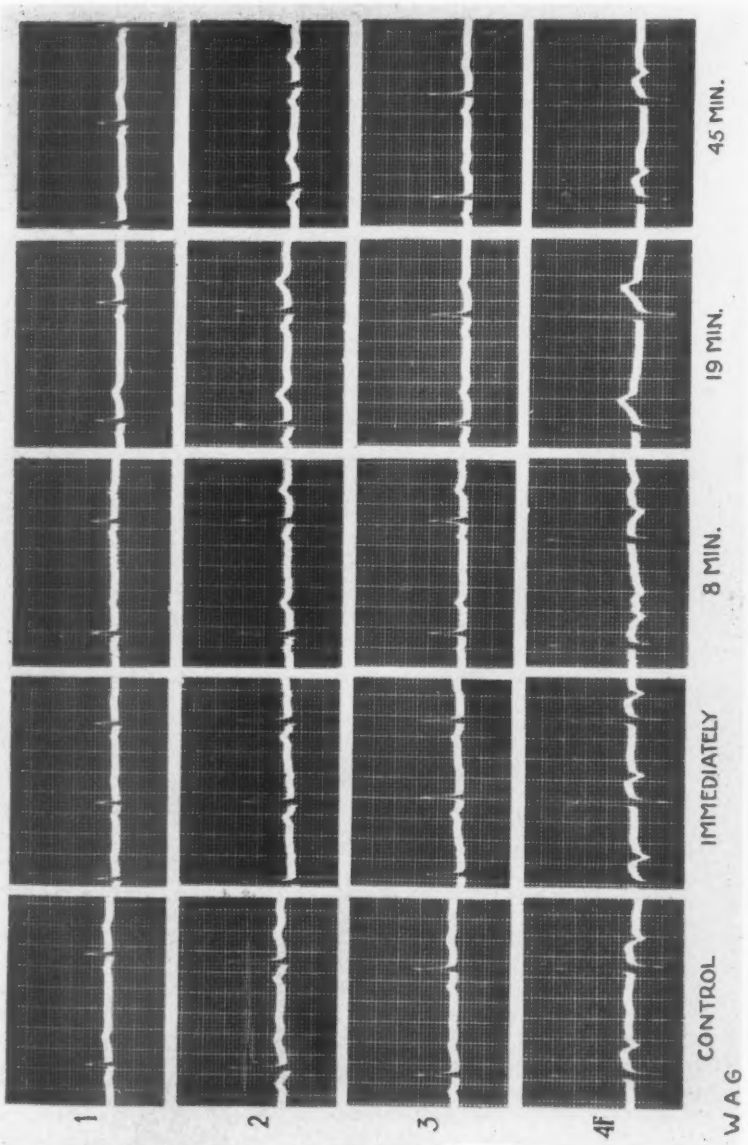

Fig. 4.—Case 2. Hyperventilation syndrome and normal heart. Control electrocardiogram made early on morning of Aug. 30, 1941, when symptoms were largely absent. Tracing taken immediately after forced voluntary hyperventilation for 30 seconds shows inversion of T_2 and T_3. Tracing taken 19 minutes after hyperventilation, during recovery, shows T waves taller than in control and an upright T in 4F. Tracings taken 45 minutes after hyperventilation, while patient was nervous and sighing, shows return of control configuration.

Electrocardiograms showed late inversion of T in all leads (Fig. 3). During his previous hospitalization, four electrocardiograms had been made (not reproduced here), the first two of which were similar to those reproduced; the third and fourth showed upright and normally tall T waves in Leads 1, 2, and 3, with diphasic T waves in the chest leads. There were no abnormalities of QRS.

A *hyperventilation test*, done after many early morning visits in an attempt to study the patient at a favorable time, when he was free of symptoms and his electrocardiogram relatively normal, produced, after 30 seconds of forced overbreathing, marked carpopedal spasm, a positive Chvostek sign, tremulousness, crushing pain over the heart, and inability to stop hyperventilating. Fig. 4 shows the control electrocardiogram and those taken after the overbreathing. Inversion of T in leads 2 and 3 occurred immediately afterward. Of especial interest is the tracing taken 19 minutes after the hyperventilation, during the recovery period, in which the T waves throughout are taller than in the control, and T in Lead IV F is entirely upright.

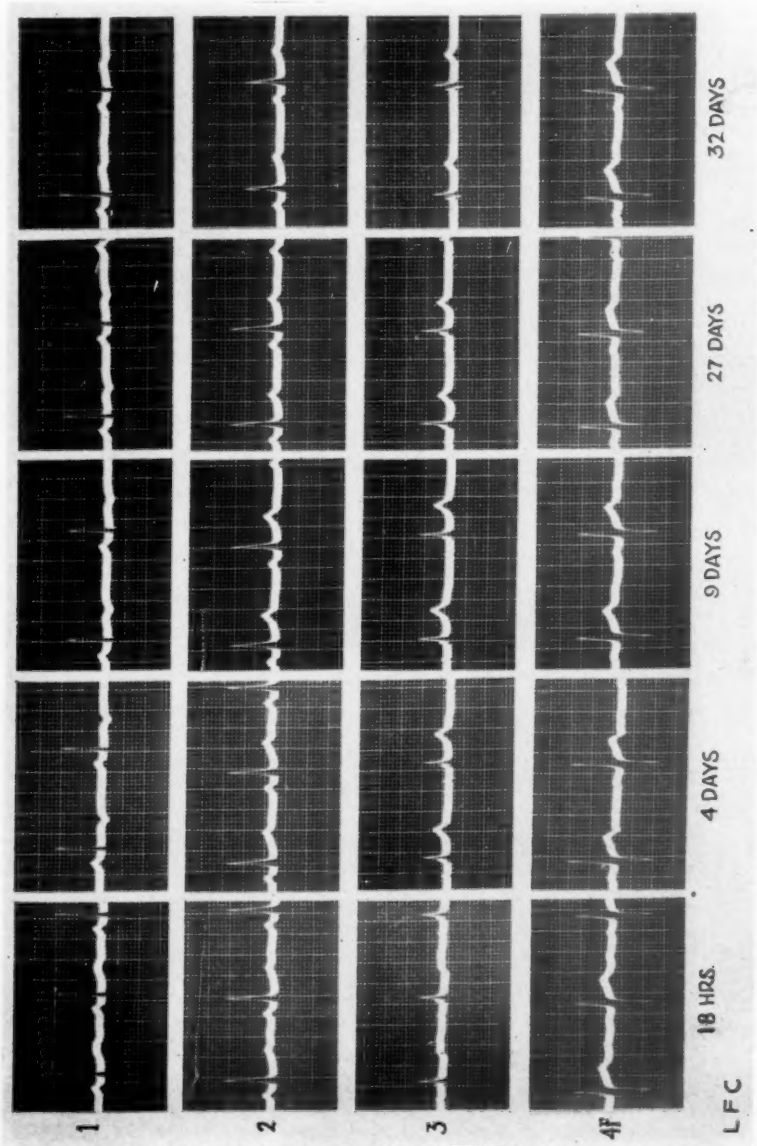

Fig. 5.—Case 3. Hyperventilation syndrome and normal heart. Serial electrocardiograms, starting 18 hours after precordial pain which was originally attributed to coronary occlusion. Note absence of QRS abnormalities.

The third patient appeared at first to have had acute coronary artery occlusion, but the correct diagnosis became apparent later, when his course was observed. His T-wave inversion (Fig. 5) was originally regarded as consistent with anterior myocardial infarction, although not entirely confirmatory, but S-T deviation and QRS changes did not appear. The tracing had returned to normal on the 32nd day, and, on the 33rd day, a hyperventilation test was performed. Although the overbreathing was carried out very poorly, a period of involuntary sighing was initiated, and his previous T-wave abnormality was reproduced (Fig. 6).

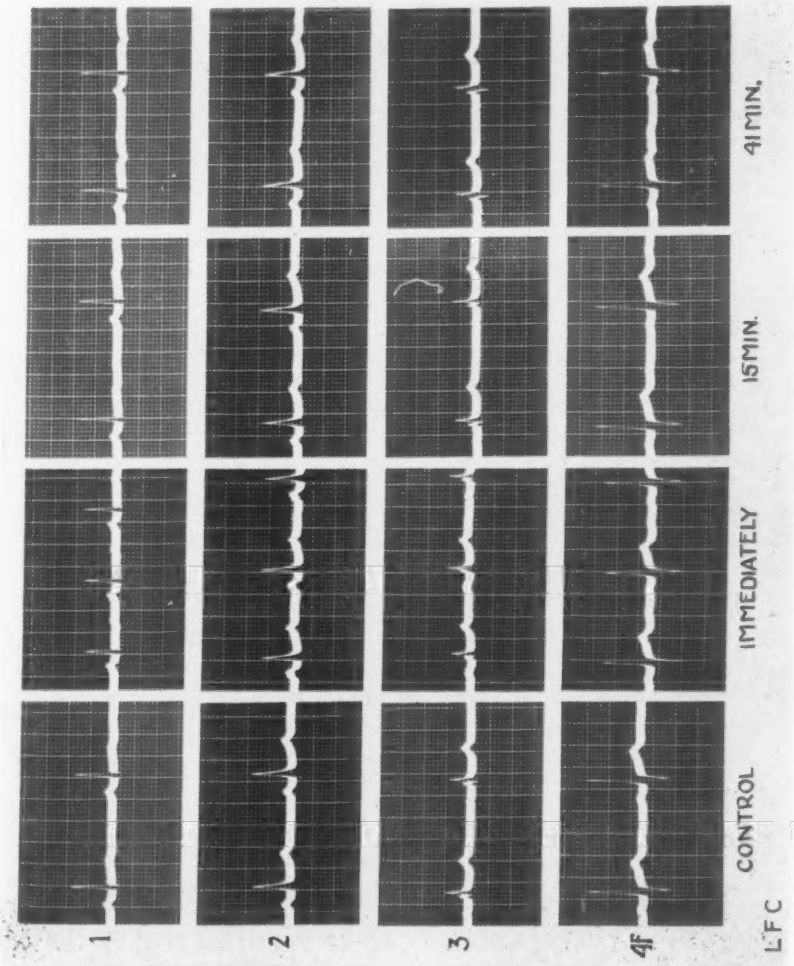

Fig. 6.—Case 3. Control electrocardiogram and hyperventilation test on thirty-third day of illness. Voluntary overbreathing poorly executed, but followed by much sighing, resulting in inversion of T; 41 minutes after start of the test.

CASE 3.—L. F. C., a man, aged 38 years, was a shipping clerk. Late in the afternoon of the day before admission to the hospital the patient ate unwisely, slept 5 hours, then awakened in a nightmare. He felt unable to get thoroughly awake,

and noted a peculiar shortness of breath, numbness and tingling, and pain over the lower part of the sternum and in the left shoulder. The pain varied in intensity in wave-like form, and became very severe, as if he "had been kicked by a horse." He was unable to breathe deeply without increasing the pain. He became weak, the whole left arm ached, and he perspired and was nauseated. The symptoms continued until he was examined 18 hours later.

Examination revealed great apprehension and slight pallor. The heart was normal. The blood pressure was 150/90. There was no congestion. The tendon reflexes were hyperactive.

Course.—After examination, 20 c.c. of aminophyllin were given into the left antecubital vein. During the injection of the solution he complained of severe pain in the left arm, with inability to move the extremity. He perspired, began to overbreathe, and complained of dizziness and numbness and tingling in the right hand. Inhalation of a carbon dioxide-oxygen mixture brought relief of all symptoms except the pain in the arm. He was unable to move the arm for several days, and was afraid to change his position in bed. He complained that his heart felt "big," and developed an extreme cardiac neurosis. His temperature was normal throughout.

Laboratory Data.—The hemoglobin was 100 per cent, the erythrocyte count, 5,240,000, and the leucocyte count, 17,800. Differential leucocyte count: neutrophiles, 66.5 per cent; lymphocytes, 28.5 per cent; monocytes, 3 per cent; eosinophiles, 2 per cent. The leucocyte count gradually fell to normal by the twentieth day. The sedimentation rate was not done until the twentieth day, when a fall of 12 mm. occurred in 88 minutes (normal, 12 mm. in 120 minutes, Linzenmeier).

The *electrocardiogram* was normal at first, then late inversion of T_1 appeared and persisted until the thirty-second day (Fig. 5). Abnormalities of QRS were not observed.

A *hyperventilation test*, performed on the thirty-third day, was preceded by apprehension, sighing, and tingling in the chest and shoulders. The overbreathing was poorly performed, but set off involuntary sighing and resulted in inversion of T_1 after 41 minutes (Fig. 6). After the test he developed tremulousness and a sense of weight over the heart.

Changes in the QRS complexes have been inconspicuous in our cases. In but a single case has the QRS change been such as to suggest the possibility of myocardial infarction, and was even then limited to the chest lead. In this instance a well-marked abnormality in QRS in Lead 4F followed a painful seizure diagnosed elsewhere as acute myocardial infarction, with return to normal by the time we were consulted. The hyperventilation test, performed because of our uncertainty about the question of infarction, produced variations in QRS in Lead 4F of a similar kind, but less in degree than those which had occurred spontaneously (Figs. 7 and 8).

CASE 4.—Mrs. L. D. W., aged 54 years, was a housewife. The history was one of a lifetime of nervousness, easy fainting, and frequent sighing respiration. Years previously her only pregnancy was terminated because she was ill with cramps and spasms in the muscles of the extremities. Twelve years before our examination her menses ceased. Thereafter she had had much nervousness, weeping, hot flashes, sudden perspiration, throbbing in the head, dizziness, exhaustion, faintness, and fainting. Injection therapy for the menopause had never been given because of her fear of the needle. Oral therapy had not been given with regularity or persistence. She had not improved as time passed, and her husband became intolerant of her invalidism, thus aggravating it.

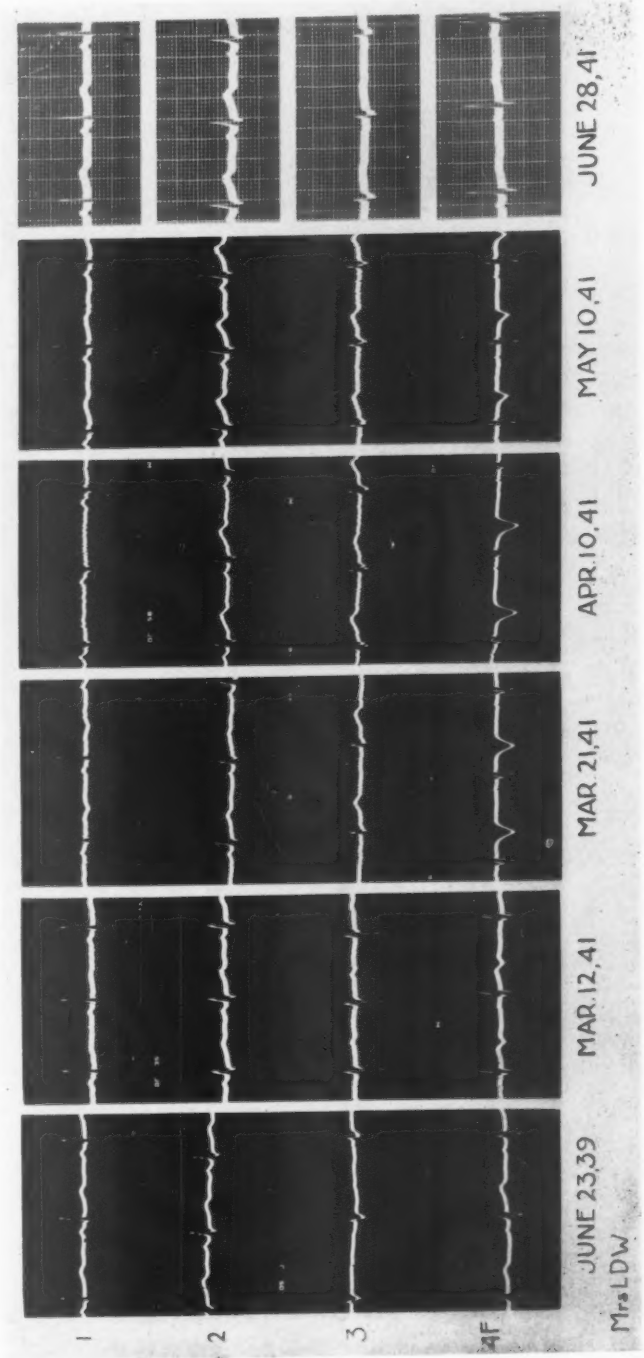

Fig. 7.—Case 4. Hyperventilation syndrome and normal heart. First electrocardiogram serves as control for serial changes after attacks of severe precordial pain and fainting, starting March 5, 1941. Note the development of W-shaped QRS in Lead 4F.

Two years before we saw her she experienced marked respiratory difficulty, in the form of a nervous catch in her breath, gasping, and extreme exhaustion. Such attacks were frequent, sometimes lasting a whole day. Many doctors were consulted, and wide differences in opinion were expressed. An electrocardiogram, taken two years before we saw her, was normal (Fig. 7, first column).

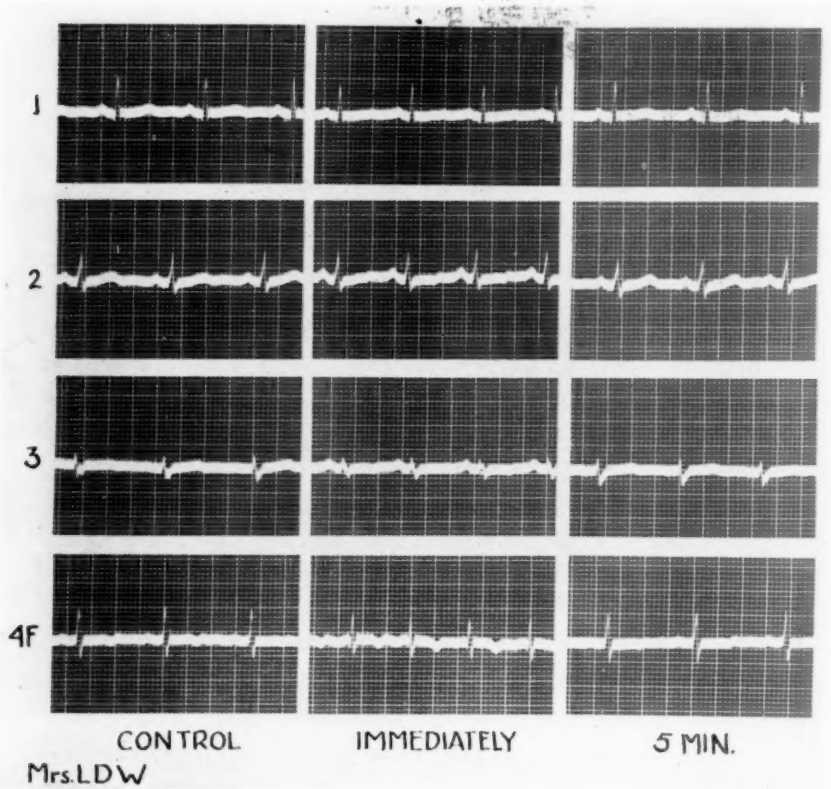

Fig. 8.—Case 4. Hyperventilation test on July 1, 1941, was preceded by yawning and lowering of T, as compared to last electrocardiogram in Fig. 7. Immediately after forced voluntary hyperventilation for 75 seconds the T waves became lower and QRS in Lead 4F became triphasic.

On March 5, 1941, three and two-thirds months before we saw her, she experienced a severe, tight pain about the left breast and xiphoid, rising to the throat, where a spasm followed. She had much difficulty in breathing, and fainted. Seven more such attacks followed in the next six days. On March 12 she consulted a physician who diagnosed heart disease. The electrocardiogram taken on that day and those taken subsequently are reproduced in Fig. 7, ending with the tracing made the day we first saw her (June 28, 1941). Hospitalization was advised on March 12, but refused. She spent most of her time in bed at home thereafter, and was never free of some kind or another of chest pain, usually in the form of a dull ache about the left breast and axilla, often interrupted by sharp, momentary, cutting sensations. Precordial tenderness was marked, and faintness was frequent. There was no fever. She developed much fear of sudden death.

Examination revealed a weeping, dejected woman who appeared otherwise healthy. The heart was normal in size, the sounds were normal, and there were no murmurs.

The blood pressure was 112/72. The lungs were normal, the jugulars were not distended, the liver was not enlarged, and edema was absent. The tendon reflexes were normal. Fluoroscopic and orthodiagraphic examination showed a heart of normal size and shape; its position and pulsation were normal. The lungs were negative.

Three days after her initial visit she returned for further study. A *hyperventilation test* was preceded by considerable yawning. The control tracing (Fig. 8) showed slight inversion of T in Lead 4F; this had been absent 3 days before, and was presumably caused by the overbreathing attending the yawning. After 75 seconds of moderately forced voluntary hyperventilation, a change in QRS in Lead 4F appeared; it resembled in kind but not in degree the changes previously observed. The small Q in Lead 4F disappeared after a dozen cycles. Lowering of T in the standard leads and deeper inversion of T in the chest lead were also noted, with return to the control conformation in five minutes. Because of the extreme anxiety of the patient, hyperventilation was not continued to the point of carpopedal spasm, tremulousness, or a positive Chvostek sign.

The next patient's electrocardiogram was normal when she was seen by us, but she had previously been told that she might have pericarditis because her T waves were low. Her hyperventilation test produced striking electrocardiographic changes, consisting of S-T depression, with lowering and inversion of T (Fig. 9), rather than the late type of inversion of T which occurred in the first four cases. This type of alteration has been more common in our cases than the more striking late inversion, and resembles the changes which occur when the test is applied to healthy subjects (Fig. 10). It is quite likely that the symptomless state of this patient at the time of her test caused her to behave like a normal person.

CASE 5.—Mrs. H. M. H., aged 38 years, was a housewife. For fifteen years the patient had had many attacks of palpitation, tachycardia, gasping respiration, dizziness, apprehension, weakness, nausea, and a clutching sensation in the left anterior axillary line. She felt cold and tremulous during the attacks. Her anxiety had been much increased when a physician expressed his suspicion that her low T waves were the result of pericarditis.

Examination was entirely negative. Sighing and objective evidence of apprehension were absent at the time of her visit. The heart was normal in size, the sounds were normal, and there were no murmurs. The blood pressure was 114/80. No congestion was found. The tendon reflexes were moderately hyperactive. Fluoroscopic examination revealed a heart of normal size, pulsating normally, and normal lungs.

A *hyperventilation test*, carried out when she was free of symptoms and at ease, was continued for 85 seconds, and resulted not only in conspicuous lowering of T in leads 1 and 2, but also in S-T depression in leads 2, 3, and 4F, and in inversion of T in leads 3 and 4F (Fig. 9). The induced symptoms and signs included dizziness, blackness before the eyes, headache, numbness and tingling in hands, a sense of dead weight in the arms, pounding of the heart, slight nausea, tremulousness, and a positive Chvostek sign. Carpopedal spasm did not appear.

Observations on Patients with Heart Disease and the Hyperventilation Syndrome.—Several patients with heart disease, who have had anxiety neuroses and the hyperventilation syndrome, have been observed. These only serve to emphasize that a diagnosis of hyperventilation

syndrome does not preclude the possibility of concomitant heart disease. One such patient, an Army colonel, 52 years of age, had acute coronary artery occlusion, with posterior myocardial infarction, which was typical in all respects, including serial electrocardiographic changes, but his symptoms after subsidence of the initial pain were those of hyperventilation, and included nervousness, sighing respiration, muscular cramps,

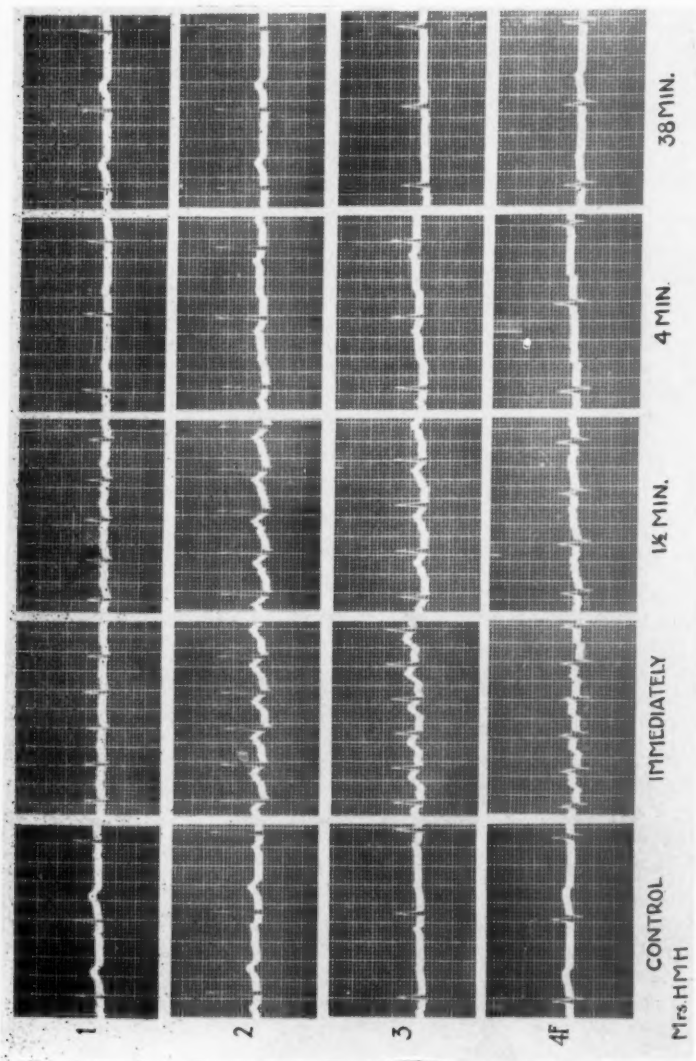

Fig. 9.—Case 5. Hyperventilation syndrome with normal heart. No symptoms preceding test. Immediately after forced voluntary hyperventilation for 85 seconds, depression of S-T, lowering of T, and inversion of T occurred. This response resembles that of healthy subjects, but is more marked.

light-headedness, and numbness and tingling of the hands, arms, and face. He became a diciplinary problem, criticised the medical officers, and frequently got himself and others into trouble. A hyperventilation test has not been carried out because his electrocardiogram still shows prominent Q waves and deep, late inversion of T in Leads 2 and 3.

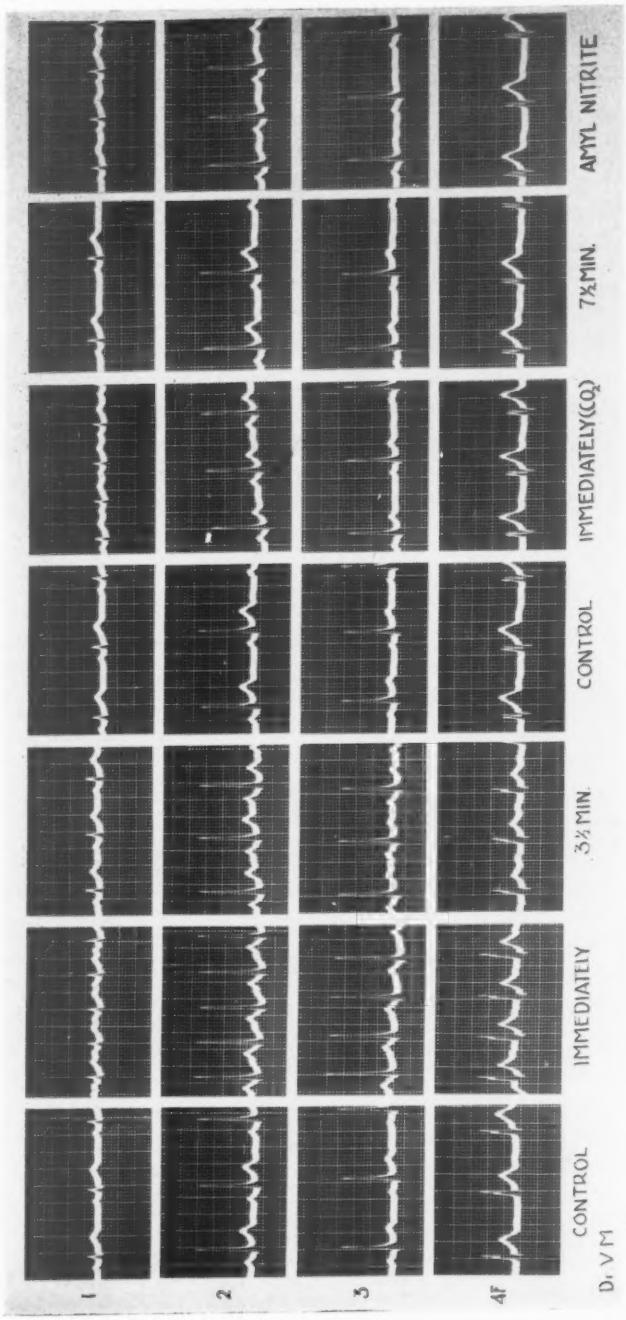

Fig. 10.—Healthy young doctor without the hyperventilation syndrome. First 3 columns illustrate effect of forced voluntary hyperventilation for 3 minutes. Immediately after the overbreathing, S-T depression and T flattening are seen. Fourth column represents control, a week later. Fifth column illustrates effect of hyperventilation for 3 minutes of a mixture of carbon dioxide and oxygen. Last column illustrates effect of tachycardia induced by inhalation of amyl nitrite.

Observations on Healthy Subjects.—The hyperventilation test was applied to six healthy young doctors. Overbreathing was continued to the point of carpopedal spasm in five of them, for which about two and one-half to three minutes were required. In all on whom the test was carried far enough, electrocardiographic changes were observed. These consisted of acceleration of rate, depression of S-T segments, and lowering or flattening of T waves in any or all leads. The most conspicuous changes were seen in Leads 2 and 3. In the first three columns of Fig. 10 a typical result is reproduced. Late inversion of T was not observed in any of the healthy subjects. The carbon dioxide combining power was normal in all, ranging between 56 and 64 volumes per cent. The pH of the venous blood before the test was normal in all, ranging from 7.35 to 7.38, with increases immediately after hyperventilation of 0.06 to 0.12; the maximum figure was 7.52. In addition to measurement of the control CO_2 combining power, measurements were at first made on blood taken after the hyperventilation, but the changes were insignificant during the short period of the tests, and the practice was discontinued.

CAUSE OF THE T-WAVE ABNORMALITIES

Overbreathing washes excessive amounts of CO_2 from the lungs and secondarily from the blood, resulting in the loss of acid ions and a shift of the blood pH in the direction of alkalinity. In our healthy subjects the maximum alkaline shift occurred at the time when the electrocardiographic abnormalities were at their maximum. The assumption is that the abnormalities are the result of alkalosis. Similar alkaline shifts have been observed during the test in some of our patients with the hyperventilation syndrome, however, without change in the electrocardiogram. In addition, well-marked, spontaneous, T-wave inversion has occurred in some of our patients at times when the pH of the venous blood was normal. These observations raise some question whether a rise in pH is the crucial factor in determining electrocardiographic change.

When CO_2 is exhaled in excessive amounts, a state of uncompensated CO_2 deficit follows. If this deficit is continued for a sufficient time (longer than 3 minutes, or less, in our tests), base is excreted in the urine, an alkaline urine is produced, and the CO_2 combining power of the blood is reduced. A state of compensated CO_2 deficit is thus produced, and the pH returns to normal. Three of our patients were admitted with CO_2 combining powers of 35, 35, and 36 volumes per cent, respectively. Two of these patients had well-marked T-wave inversion when the combining power was low, and one of them exhibited only minimal depression of S-T in Leads 1 and 4F. Two of them were studied later, when the combining power had risen to 48 volumes per cent, at which time the electrocardiograms were unchanged. Unfortunately, some of our patients with the most striking electrocardio-

graphic abnormalities were observed early in the course of the study, before chemical observations were being included. At present it appears that neither the degree of alkaline shift nor the extent of lowering of the CO_2 combining power is the sole factor in determining the kind or magnitude of the S-T and T changes. Much more study is necessary before this is established, however. Even if one of these factors is subsequently found to be the important one, the exact mechanism by which it operates in altering the electrocardiogram must still be explained.

Barker, et al.,[8] have shown that the hyperventilation of air from a large dead air space, by means of which the removal of excessive amounts of CO_2 from the lungs and blood may be prevented, will result in no tetany and no change in the electrocardiogram. Soley and Shock[4] relieved the symptoms of their patients by the administration of atmospheres containing 2 to 5 per cent of CO_2. Fig. 10 illustrates a similar experiment on one of our healthy subjects. In the fourth column is the control tracing, made a week after the hyperventilation test illustrated in the first three columns. Forced hyperventilation with a mixture of 5 per cent CO_2 and 95 per cent oxygen was carried on for 3 minutes. The experiment was not conducted too satisfactorily because the subject breathed through a loose-fitting face mask which allowed an insufficient flow of about 12 liters of gas mixture per minute. The experiment led to slight tetany (much less than during the previous experiment), with a pH change from 7.40 to 7.48, which was again much less than before. S-T depression did not occur, although the T waves in the standard leads did become slightly lower. It is reasonable to assume that, had the experiment been conducted under more ideal circumstances, both the tetany and T-wave changes would have been absent.

In the normal subjects and in many of the patients who were tested after recovery from the syndrome, S-T and T alterations were never observed in the absence of appreciable increases in heart rate. In these subjects, depression of S-T, especially in Leads 2 and 3, was more conspicuous than flattening of T, and late inversion of T was never observed. A good example of this is illustrated in Fig. 10. To study the effect of acceleration of the heart rate without hyperventilation, we administered amyl nitrite by inhalation to two subjects, and 2.6 mg. ($\frac{1}{25}$ grain) of atropine sulphate by vein to another. The resulting changes were similar to those produced by hyperventilation. In Fig. 10 the effect of amyl nitrite on a healthy subject is illustrated in the last column. Although the acceleration was not as great as that after hyperventilation, the result is obviously similar.

Acceleration of rate is not the cause of the conspicuous late inversion of T shown in Figs. 1, 3, 5, and 7, which illustrate cases in which T-wave negativity appeared spontaneously. It is wholly possible that acceleration is the cause of the S-T depressions, but not of the late inversion of T.

DISCUSSION

It is evident that patients with the hyperventilation syndrome at times show conspicuous, late inversion of the T waves. Others show S-T depression and pronounced lowering of T, possibly through the mediation of acceleration of rate. Rarely, QRS abnormalities may be observed.

The ramifications of this are considerable in cardiovascular medicine, for the syndrome often includes severe precordial pain which suggests the possibility of coronary artery occlusion. The symptoms, plus the electrocardiographic abnormalities, must make the physician careful not to be led to an erroneous diagnosis of myocardial infarction, with its resulting accentuation of the already severe anxiety neurosis. Although the electrocardiographic abnormalities are distinctly not those of myocardial infarction, they have nevertheless frequently been so interpreted in the cases we have seen, and we ourselves have made the error.

The Possibility of Heart Disease.—The possibility that our patients, especially those with late inversion of T, actually suffered minor infarctions which did not produce ordinary patterns, and that the hyperventilation syndrome was simply an added factor, cannot be lightly dismissed. Barach et al.,[9] have cited the work of others[10, 11, 12, 13, 14] and pointed out that alkalosis produces vasoconstriction. They have shown, also, that the experimental inhalation of low-oxygen atmospheres is attended by hyperventilation and an alkaline shift. When patients with the anginal syndrome are subjected to low-oxygen atmospheres and develop S-T and T deviations, it is possible that the deviations are due to vasoconstriction produced by alkalosis. Such a mechanism, it must be admitted, could operate in our cases; the vasconstriction might reduce the blood supply to the myocardium sufficiently to reproduce the spontaneous electrocardiographic patterns. It is our belief, however, that our patients have normal hearts. We have no final proof that the hearts are structurally normal, for all of the patients are still living. Against the presence of coronary artery disease are the relative youthfulness of most of them (the youngest who was thought not to have heart disease was 25 years old, the oldest, 62 years; average, 40.5 years), the fact that 10 are women, that none had hypertension, and that none had fever after spontaneous attacks.

Leukocytosis and an increase in the sedimentation rate were observed in two cases. Whether or not such changes can be produced by alkalosis is now under consideration.

Frequency of Electrocardiographic Abnormalities.—In only six of the 25 persons were all of the electrocardiograms normal. We suspect that most patients with the syndrome, if not all, will exhibit abnormalities if tracings are taken at the proper time. It is likely that changes would be conspicuous when the blood pH has been shifted

markedly toward alkalinity, still more conspicuous when an alkaline shift occurs in a patient who has already lost an appreciable amount of his alkali reserve, and entirely absent in a patient whose electrocardiogram is not taken until he has recovered from his symptoms and the dislocation of his acid-base balance. Case 1 is such an example; the control tracing in Fig. 2 was entirely normal (with the patient at ease), and all tracings which showed inversion of T were taken when he was frightened by the procedure (Fig. 1). It is further likely that the hyperventilation test will fail to reproduce electrocardiographic abnormalities in striking degree when recovery from the syndrome has been allowed to progress too far.

Hyperventilation in Other Conditions.—It is only reasonable that hyperventilation may be a factor in the genesis of symptoms in a wide variety of diseases when the element of anxiety is added. Such an example is the Army colonel, whose symptoms, after subsidence of the initial pain of coronary artery occlusion, were clearly those of anxiety and hyperventilation. Case 4 is that of a menopausal woman who suffered also from hyperventilation.

Scherf[15] has attributed S-T depression and T negativity to the menopause. His tracings were similar to ours, and returned to normal when estrogenic therapy relieved the symptoms of the menopause. It is not impossible that his electrocardiographic deviations were, in fact, the result of hyperventilation.

Graybiel, Starr, and White[16] reported S-T and T changes after the inhalation of tobacco smoke. Their electrocardiograms are similar to ours. We have had the opportunity to observe them conduct one of their tests, during which the smoke of one to three cigarettes was inhaled as rapidly and deeply as possible. Hyperventilation may have been responsible for the electrocardiographic changes.

SUMMARY

1. Patients with anxiety neuroses and the hyperventilation syndrome frequently exhibit marked electrocardiographic abnormalities, consisting either of late inversion of T, or of S-T depression with marked lowering of T. Any or all leads may be involved. QRS changes have been observed in but a single case and were limited to Lead 4F.

2. The abnormalities disappear when recovery from the syndrome takes place, but may be reproduced by voluntary hyperventilation if recovery has not become too firmly established.

3. Evidence is presented to suggest that the abnormalities are the result of alkalosis, but certain discrepancies raise some question whether this is the sole factor.

4. Since severe precordial pain may be included in the syndrome, recognition of these marked electrocardiographic abnormalities assumes importance, lest they be attributed to infarction of the heart, with the result that the anxiety neurosis becomes worse.

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DISCUSSION

DR. FRANCIS L. CHAMBERLAIN, San Francisco, Calif.—Dr. Thompson has shown very well the changing electrocardiograms of nervous people with nervous hearts. However, it should be emphasized that there are mechanisms other than hyperventilation that may be responsible for electrocardiographic changes of this type. Dr. Paul White, Dr. Ashton Graybiel, Miss Ola Nagle and I have found that hyperventilation is one of several mechanisms.

Variation in the position of the diaphragm is of importance. Thus, deep inspiration or the sitting position lowers the diaphragm, and, in so doing, may invert T waves, especially in Leads 2 and 3.

Apprehensive persons often breathe during periods of excitement in such a way that their reserve air is greatly increased at the expense of their complemental air, thus lowering the diaphragm. This may be an important factor.

In some patients hyperventilation may similarly lower the diaphragm.

Autonomic nervous system imbalance also appears to result in T-wave abnormalities, as shown by the effect of epinephrine, atropine, ergotamine, and acetyl-β-methylcholine.

It is well to remember that hyperventilation may reverse T waves when the heart is abnormal. Two of our patients in the past three years, who had normal electrocardiograms which became abnormal with hyperventilation, both of them obviously patients who fitted into this so-called hyperventilation syndrome, have since died very suddenly, and the autopsies showed that death was the result of coronary disease.

Clinical Reports

TRICUSPID STENOSIS AND PULMONARY STENOSIS COMPLICATING CARCINOID OF THE INTESTINE WITH METASTASIS TO THE LIVER

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TRICUSPID stenosis is usually found in association with other cardiac lesions, particularly with valvular disease of the left side of the heart. As an isolated lesion it is considered a clinical curiosity, and in association with pulmonary stenosis it is even more uncommon.

Among the 194 collected cases of tricuspid stenosis of Leudet,[1] J. B. Herrick,[2] Griffith,[3] W. W. Herrick,[4] and Futcher,[5] only three instances of tricuspid stenosis and pulmonic stenosis without involvement of the other valves were reported. In 1880, Osler[6] presented a case. Cabot[7] reviewed 33 cases of tricuspid stenosis in association with other valvular lesions. There were two cases of stenosis of the tricuspid and pulmonary valves. Castellanos and his associates[8] have also described a case.

The clinical aspects and circulatory dynamics of tricuspid stenosis have been adequately described by Friedlander and Kerr,[9] Altschule and Blumgart,[10] Altschule and Budnitz,[11] and Kerr and Morrison.[12] In 34 cases of tricuspid stenosis the diagnosis has been made clinically.

Because of the rarity of the combination of tricuspid and pulmonary stenosis without other valvular lesions, and the difficulties encountered in diagnosis, it is felt that this case is worthy of record.

CASE REPORT

B. K., a 44-year-old woman, married for 23 years, who had had five full-term pregnancies without any untoward manifestations, was admitted to the Jewish Hospital Oct. 11, 1940, with a history of weakness and increasing fatigue for the preceding seven years, dyspnea for five years, swelling of the abdomen and lower extremities for two years, and cough for four days.

Her family history was noncontributory. There was no history of rheumatic fever, tonsillitis, or other infectious diseases.

Eight and a half years previously she had several attacks of pain in the epigastrium and right upper quadrant of the abdomen, radiating to the back, and associated with nausea and vomiting. One year later, during her pregnancy, she had another attack which was diagnosed as gall bladder disease. No cardiac or hepatic disorder was noted at this time.

(We are indebted to the Beth Israel Hospital, of New York, for the following history and data, most of which were obtained after the patient's death.)

From the Jewish Hospital of Brooklyn, Medical Service of Meyer A. Rabinowitz, M.D.
Received for publication April 4, 1941.

On Jan. 14, 1936, she was admitted to the Beth Israel Hospital with the complaint of fatigue of two and one-half years' duration. This occurred after her last pregnancy (1933), when she noted increasing fatigue—she was "run down" and "washed out." Her ability to do her everyday work had definitely decreased. She had never been disturbed by climbing two flights of stairs, but now found herself quite exhausted, very short of breath, and disturbed by the rapid beating of her heart. She could not stand for any length of time without support. The fatigue and breathlessness increased. Two months before admission she had generalized itching; this lessened considerably just before entering the hospital. Her physician, whom she consulted three weeks prior to admission, said she had some form of "heart trouble." He did not notice any hepatic enlargement. There was never any jaundice. She had lost 10 pounds in the two years prior to her admission. She also was possibly in her climacteric period, for her menstruation was irregular and she had vasomotor phenomena.

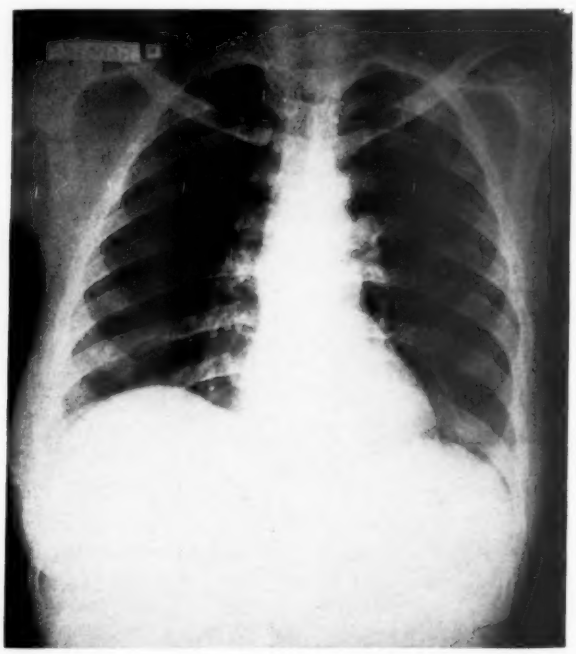

Fig. 1.—Teleroentgenogram of chest taken Jan. 16, 1936. The heart is normal in size and shape. The lungs are clear.

Examination at that time showed a normal pulse rate, temperature, and respiratory rate. She did not appear acutely ill and she showed no dyspnea. The sclerae were slightly icteric. There was a peculiar flushing which varied greatly with emotional changes. This, the patient stated, she had had for as long as she could remember. There were numerous excoriations over the entire skin surface, especially the trunk. There was no engorgement of the veins of the neck. The lungs were normal. The cardiac apex impulse was barely palpable 8.5 cm. from the midsternal line. Normal sinus rhythm was present. At the apex there was a systolic murmur. In the pulmonic area there was a harsh systolic murmur which occupied most of systole. These murmurs were recorded phonocardiographically. The pulmonic systolic murmur was said to be audible in the left interscapular area, but this was not confirmed phonocardiographically. The pulses were regular and of good quality. The blood pressure was 102/78. Examination of the abdomen revealed no ascites or collateral circula-

tion on the anterior surface; there were, however, some dilated veins over the lower part of the back. The liver was enlarged, extending to the umbilicus. The mid-portion of the anterior surface was extremely convex and felt somewhat cystic. The spleen was not felt. There was no edema of the lower extremities, and there was no clubbing of the fingers or toes.

Roentgenograms of the chest, taken Jan. 17, 1936, showed that the lungs were normal. The heart was normal in size, shape, and position. The roentgenokymogram was normal. The aorta appeared elongated. Oblique views showed no auricular or ventricular enlargement. Roentgenograms of the abdomen showed the large mass in the right upper quadrant. The gall bladder was displaced, but its function was normal. Excretion pyelograms showed nothing except a displaced right kidney. The electrocardiogram was normal, except for low voltage; the rate was 79, and left axis deviation was present. The urine was negative. The erythrocyte count was 4,000,000, with a hemoglobin of 65 to 75 per cent. The venous pressure was 6 cm. The icteric index was increased. The cholesterol was 263 mg. per 100 c.c. of serum. The arterial blood carbon dioxide content was 43.0 per cent. The oxygen saturation was 92.4 per cent. The venous blood carbon dioxide content was 48.7 per cent, and the oxygen saturation, 67.4 per cent.

On her fourteenth day in the hospital the patient developed fever and became markedly jaundiced. Her liver increased in size. Operation was advised, but she refused, and was discharged Feb. 6, 1936, with a diagnosis of hepatomegaly of unknown origin.

She was readmitted for operation Feb. 23, 1936. A diagnosis of cyst of the liver was made. On Feb. 24, 1936, drainage of numerous cystic cavities was performed. The bloody tissue that was obtained gave the appearance of liquefaction necrosis of liver tissue. On the posterior surface of the liver, just below the point at which the liver becomes extraperitoneal, corresponding to the junction of the hepatic vein and vena cava, there was a firm mass about the size of a half dollar and approximately 1 cm. in thickness. It looked like a malignant tumor, but it could not be excised because of its position. The pathologic report was "bloody fluid with necrotic material." She was discharged April 11, 1936.

(We are indebted to the Beth David Hospital for the following data.) She entered the Beth David Hospital Oct. 25, 1937, with a purulent discharge from a sinus at the site of the operation. She was again operated on, and a huge abscess cavity was found and drained. The pathologist reported suppurating granulating tissue. Lipiodol and thorotrast studies confirmed the presence of the cavity. She was given emetine therapy while in the hospital, and was discharged in an improved condition Dec. 5, 1937.

The patient was confined to her bed therafter. There was a gradual onset of edema of the lower part of the body and extremities, which became markedly indurated. For eight months she received digitalis and 2 c.c. of mercupurin intravenously every three or four days, and then intramuscularly. A few days before admission she "caught cold," and, because of a cough and increasing dyspnea, she was admitted to this hospital. She had lost 25 pounds in the five months preceding her admission.

On admission the temperature was 100.2° F.; the pulse rate, 100; the respiratory rate, 32; and the blood pressure, 78/60. She was poorly nourished and appeared chronically ill. She had a peculiar, reddish-purple cyanosis—a violaceous color—most marked over the malar areas, with a butterfly configuration, and a mottled formation over the rest of the body. She seemed to be pigmented, but pressure obliterated all color, which readily returned.

She spoke with a weak, but husky, voice. The vocal cords showed hyperemia. The neck veins were markedly engorged and prominent. There was no tracheal tug.

The fundi were normal. The lungs were resonant throughout. There were fine râles at the base of the right lung. Medium moist râles and rhonchi were heard over the whole of the chest posteriorly, and in the axillae. The veins over the anterior chest wall were dilated.

Percussion showed that the heart extended to the left anterior axillary line. The apex beat was not felt. Inconstant, rough, systolic and diastolic murmurs were heard at the apex. A roughened systolic and a short blowing diastolic murmur were heard at the aortic area. The right brachial and radial pulsations were absent; the left brachial pulse was strong.

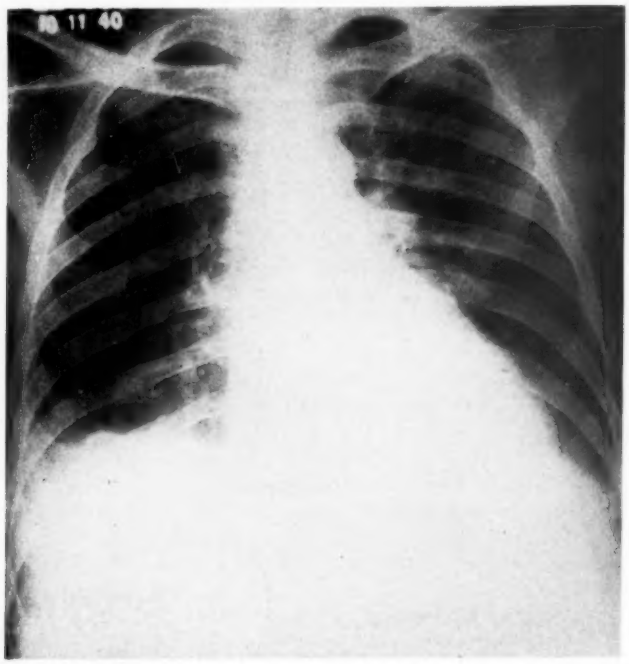

Fig. 2.—Teleroentgenogram of chest taken Oct. 11, 1940. There is slight cardiac enlargement. The lungs are not remarkable.

There was marked edema of the abdominal wall. A well-healed, large scar was present in the right upper quadrant. The liver was two fingerbreadths below the costal margin. It did not pulsate. Pressure on the liver did not increase the size of the veins of the neck. There was marked edema over the sacrum.

The lower extremities showed mottled cyanosis and extreme edema. The arms and forearms were tense from edema. The extremities were of normal temperature.

Fluoroscopic and radiographic examination of the heart was rather difficult because of the patient's precarious condition. Under the fluoroscope it was noted that the amplitude of the pulsations of the left and right ventricles was not appreciably impaired, and no gross auricular enlargement could be demonstrated. There was no evidence of calcification of the pericardium. There was a small amount of fluid in the right costophrenic sinus; the lung fields otherwise were clear. Her condition did not permit radiopaque visualization of the cardiac chambers by the Robb-Steinberg technique.

The electrocardiogram on Oct. 11, 1940, showed a ventricular rate of 100, normal sinus rhythm, and a P-R interval of 0.16 second. The main deflection and the T wave

were isoelectric in Lead I. Lead IVF was normal. The entire tracing showed extremely low voltage. The electrocardiographic diagnosis was severe myocardial involvement. Another tracing, made on Oct. 23, 1940, showed no change.

Laboratory Data.—The blood Kline reaction was negative. No methemoglobin or sulfhemoglobin was demonstrated spectroscopically. Blood: urea nitrogen, 26.4 mg. per 100 c.c. serum; icteric index, 10.6; phosphorus, 2.6 mg.; phosphatase, 14.2 units; chlorides, 388 mg.; sodium, 312 mg.; potassium, 18.1 mg.; cholesterol, 78.4 mg.; free cholesterol, 42.0 mg.; free cholesterol, 50 per cent; total protein, 4.65 Gm.; albumin, 1.96 Gm.; globulin, 2.69 Gm.; serum A./G. ratio, 0.73. The prothrombin time was 14.4 seconds. Urine: specific gravity, 1.022 to 1.018; one-plus albumin and an occasional leucocyte. The sedimentation time was 70 mm. per hour. The hemoglobin was 56 to 67 per cent; the erythrocyte count, 2,700,000; and the leucocyte count, 7,000 to 9,800. *Circulation Studies*, Oct. 28, 1940: Venous pressure (jugular vein), 20.4 cm. of water; saccharine time, neck-to-tongue, sixteen seconds; ether time, neck-to-lung, seven and one-half seconds.

Except for one day of fever, just before death, the patient ran an afebrile course. She was drowsy most of the time. The administration of oxygen produced no apparent improvement. She became weaker and more stuporous and died after three and one-half weeks in the hospital.

Discussion.—There was great difficulty in arriving at a satisfactory diagnosis. It was apparent that the patient was suffering from a tricuspid type of congestion; i.e., the inflow type of Volhard, the hypodiastolic type of Fishberg, or, as Pollitzer described it, a paracardial adiastolic congestion.

Because of the intense cyanosis, consideration was given to pulmonary artery sclerosis and endarteritis proliferans and pulmonic stenosis. Functional incompetence of the tricuspid valve is usually associated with lesions of the left side of the heart or conditions marked by increased tension in the pulmonary circuit. There were no indications that any of these factors were present. Organic tricuspid stenosis is usually associated with mitral stenosis. There was no evidence of the latter, and the right auricle was not enlarged. There was some evidence to support the clinical concept of constrictive mediastinopericarditis. However, there was no calcification of the pericardium and there was no reduction in the amplitude of the pulsations of the right and left ventricles. Chronic, fibrous, parietal myoendocarditis could produce the same picture. Consideration was also given to primary tumor of the auricle and secondary neoplastic disease, with involvement of the superior and inferior cava and right auricle.

Autopsy.—The following are the important pathologic changes:

The pericardial cavity contained approximately 60 c.c. of a clear, amber fluid. The pericardium was smooth and glistening and in no place constricting. The superior and inferior venae cavae were patent throughout. The heart measured 10 cm. across the base and 9.8 cm. from apex to base. It weighed 220 Gm. The apex was pointed and made up of the left ventricle. The epicardium was smooth and glistening. The right atrium was distended with post-mortem blood clot. Its endocardium was pearly gray; this involved the entire wall and spread between the muscle bundles

of the auricle. There was a firm, raised, gray plaque just proximal to the right atrioventricular orifice. The right atrioventricular orifice was shaped like a fish mouth, and barely admitted the tip of the little finger. The valve leaflets were fused, and the free margins were greatly thickened. They were pearly gray, firm, and inelastic. The right atrioventricular orifice measured 4.5 cm. in circumference. The chordae tendineae were fused, shortened, and thickened. The right ventricular wall measured less than 0.7 cm. in thickness. The papillary muscles were small and

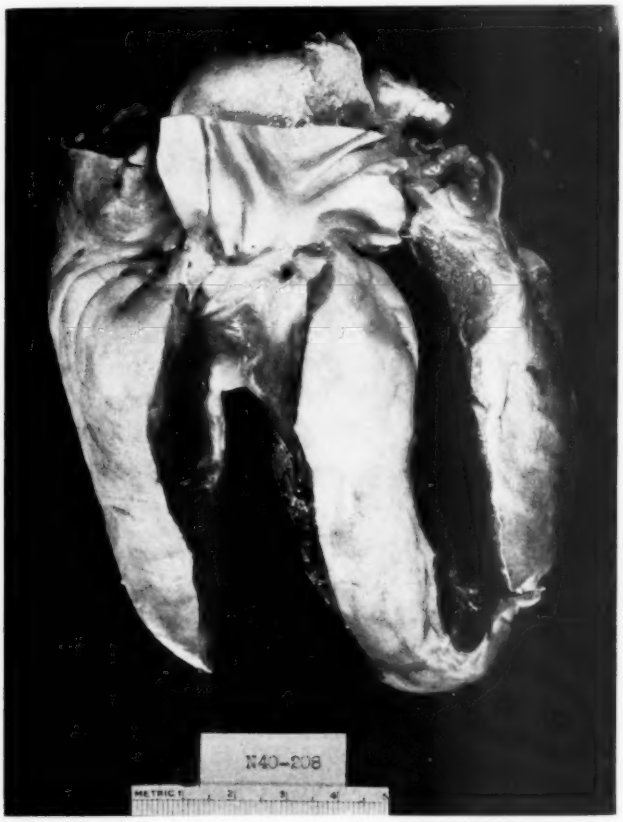

Fig. 3.—Photograph showing stenosis of the pulmonary valves. There is hypertrophy of the right ventricular myocardium.

flattened. The pulmonary orifice was similarly stenosed, and admitted little more than the tip of the probe. When spread out, it measured 3 cm. in circumference. The valve leaflets which were distinguishable were pearly gray, rigid, and fused. There was no evidence of patency of the ductus arteriosus or the foramen ovale. The left atrium was dilated, and the musculature was flattened. The endocardium was opaque, soft, and gray. The left atrioventricular orifice measured 9 cm. in circumference; its leaflets and chordae tendineae were delicate. The wall of the left ventricle measured 1.5 cm. in thickness. The aortic orifice measured 7.5 cm. in circumference; the valves were delicate and fenestrated.

Microscopic section showed fibrosis of the tricuspid and pulmonary valves and of the endocardium of the right auricle. There were splitting and reduplication of the elastic layer, with the formation of dense, fibrous, collagenous connective tissue.

Evidence of a previous inflammatory lesion was seen at the rings of the tricuspid and pulmonary valves, as manifested by new blood vessels and occasional round-cell infiltration.

The ileum presented numerous nodular masses, rather firm in consistency, and yellow brown in color. These on section revealed the typical appearance of argentaffine cell neoplasm. Metastases to the regional mesenteric lymph nodes and several to the liver were found. The metastasis in the liver was broken down, pseudocystic, and contained hemorrhagic and tumor tissue.

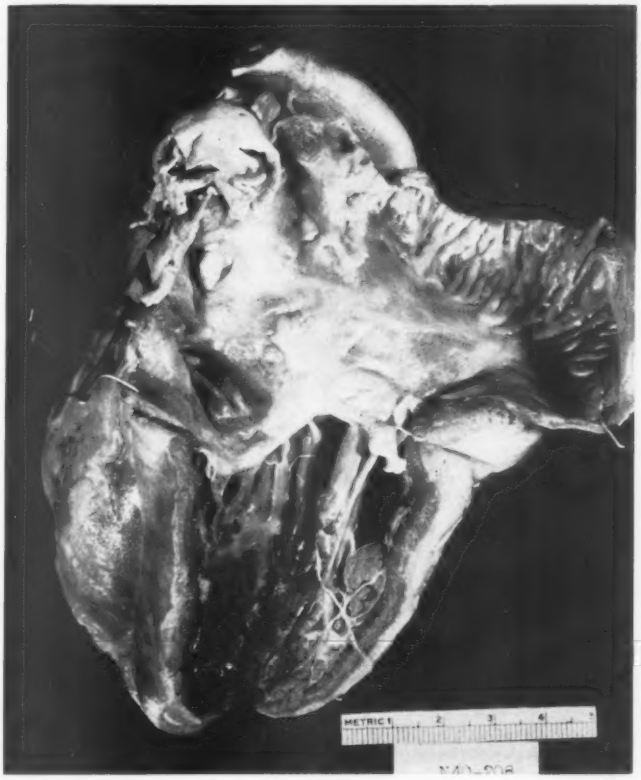

Fig. 4.—Photograph showing stenosis of the tricuspid valve with fibrous endocarditis of the right auricle.

COMMENT

The diagnosis of tricuspid and pulmonic stenosis was not made because of the unusual clinical and roentgenologic phenomena. The marked fibrous endocarditis of the right atrium prevented the dilatation and hypertrophy of that chamber which is commonly associated with tricuspid stenosis. In pulmonic stenosis, besides the valvular defect, right ventricular hypertrophy and dilatation are usually found. It is quite probable that the marked tricuspid stenosis impeded the blood flow to the right ventricle to such an extent that the work of the ventricle was decreased.

Carcinoids of the intestine are polypoid growths which contain groups of epithelioid cells, cuboidal or cylindrical, granular and argentaffine, arranged in small groups or in broader bands. The uniform size, regular position, opacity, and lack of hyperchromatism indicate only moderate malignancy. Metastasis, which is uncommon, takes place in the mesenteric lymph nodes and liver.

CONCLUSION

A case of tricuspid stenosis and pulmonary stenosis, with fibrous endocarditis of the right auricle, is reported. This combination without other valvular defects is exceedingly rare, and the association with right auricular mural endocarditis is unique. The cause of the inflammatory process was not ascertained.

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832 OCEAN AVENUE

RIGHT-SIDED HEART FAILURE (COR PULMONALE) CAUSED BY CHEST DEFORMITY

Case Report

A. J. Hertzog, M.D., and W. R. Manz, M.D.
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DEFORMITY of the thorax as a cause of right ventricular failure is rare. Most of the reported cases are in the older French and German literature. Corvisart,[1] as early as 1806, performed an autopsy on a hunchback who died with symptoms of cardiac failure and found dilatation of the right auricle and ventricle. He attributed this to the increased resistance offered by the distorted blood vessels in the chest. Finley,[2] in 1921, remarked on the "almost complete absence" in English medical literature of any reference to the effects of scoliosis on the thoracic viscera. He reported 4 cases of extreme deformity of the thorax, resulting in hypertrophy and dilatation of the heart, with cardiac insufficiency. The left ventricular hypertrophy which he found in addition to the right ventricular hypertrophy in two of these cases was attributed to constriction of the aorta from the sharp curves resulting from the deformed vertebrae. Bachmann,[3] in 1899, reported a detailed study of 197 patients with severe scoliosis and kyphosis that came to autopsy. He noticed that displacement of the heart upward and in the opposite direction to the scoliosis was a very frequent occurrence. Death was caused by heart failure in 116 (59.4 per cent) of these cases, but in 72 it was secondary to pulmonary disease rather than to the chest deformity alone. A number of isolated reports have been published. For a review of these cases, one is referred to the papers by Boas[4] and Edeiken.[5] Reid,[6] in 1930, reported the case of a 16-year-old girl who died of cardiac hypertrophy and dilatation caused by a chest deformity of fourteen years' duration. Chapman, Dill, and Graybiel,[7] in 1939, in a complete review of the subject, were able to collect from the literature 126 cases of fatal heart failure caused by chest deformity. They added 4 cases of their own. Clawson[8] found, in the records of the Department of Pathology of the University of Minnesota from 1910 to 1938, inclusive, 69 cases of primarily right-sided failure among 4,678 cardiac deaths. Four of these 69 cases were instances of chest deformity. Hallock and Rigler,[9] in 1941, in a clinical series of 38 cases of cor pulmonale, found one in which there was a thoracic deformity. This was in a 17-year-old hunchback.

The following case is reported because of its rarity and the necessity of recognizing deformity of the chest as an etiologic agent in certain cases of heart failure.

From the Luther Hospital, Eau Claire.
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CASE REPORT

A 27-year-old woman was admitted to Luther Hospital in an orthopneic, markedly cyanosed condition. She had had increasing dyspnea on exertion for several months, and occasional attacks of palpitation in the preceding three or four years. One month before admission she suddenly became more cyanotic, dyspneic, and fatigued. The patient had poliomyelitis at the age of four years, but recovered completely, with no residual paralysis. At the age of nine years she severely injured her shoulder and neck in a fall from a grandstand. This was followed by gradual elevation of her right shoulder, with the later development of marked kyphoscoliosis. An orthopedic consultant at the time regarded the deformity as traumatic in origin. She remained a semi-invalid.

Fig. 1.—Roentgenogram of chest taken post mortem, showing severe chest deformity.

Physical examination revealed a small woman who weighed approximately 90 pounds. Her temperature was 99.2° F., and her pulse rate was 124. Her blood pressure was 98/65. The thorax was markedly deformed by scoliosis, and there was an anteroposterior convexity. She was cyanotic, markedly dyspneic, and in a critical condition. There was no edema or ascites. Examination of the heart revealed distant sounds with an increased rate. No murmurs were heard. A few moist râles were present at the bases of both lungs. The liver was enlarged; it extended several centimeters below the costal margin. The remainder of the examination did not reveal any important abnormalities. Urinalysis was negative except for one-plus albumin. No other laboratory work was done.

The clinical diagnosis was acute heart failure, and routine treatment was initiated. However, she did not respond; the dyspnea and cyanosis increased, and she died the day after admission.

Autopsy.—The body was 150 cm. in length, and its weight was estimated at 90 pounds. The chest was markedly deformed. There was marked cyanosis of the entire face and neck. Edema was absent. Examination of the abdominal cavity revealed approximately 100 c.c. of straw-colored fluid and downward displacement of the liver. It extended 11 cm. below the right costal margin. The pleural cavities contained no fluid or adhesions. There was marked deviation of the midthoracic spine to the right, associated with lateral rotation and kyphosis. There was also a lateral rotation to the left of the lumbar vertebrae, with anterior displacement of the lower thoracic vertebrae. The ribs of both sides, particularly on the right, showed considerable displacement. The pericardial sac had a transverse diameter of 11 cm.; it contained no excess fluid.

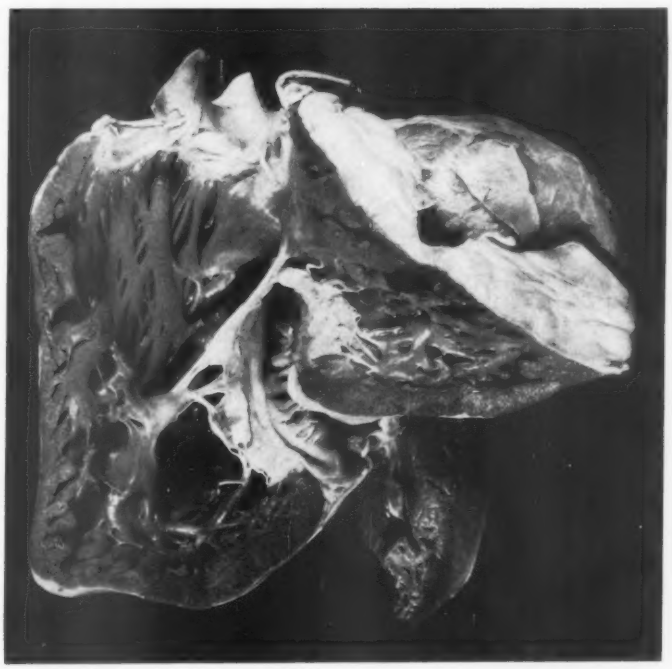

Fig. 2.—Marked hypertrophy and dilatation of the right ventricle.

The heart weighed 200 Gm. The epicardial surfaces appeared normal. There was marked hypertrophy of the right side of the heart. The right ventricle and right auricle were considerably larger than the left. The right ventricular wall was markedly hypertrophied; it measured 1.3 cm. in thickness. There was also considerable dilatation of the right ventricle (Fig. 2). The left ventricle appeared to be of normal size. The appendages, endocardium, and valves showed no abnormalities. The septum was reddish brown in color and showed no streakings. The root of the aorta appeared normal. The coronary arteries were patent and showed a minimum of sclerosis.

The right lung weighed 200 Gm., and the left, 300 Gm. Both lungs were displaced anteriorly. The lungs were grayish pink in color and showed a minimum of anthracosis. There was no apical scarring. The consistency of the left lung was

greatly increased. There was no evidence of emphysema. On section, both lungs were dark red and showed considerable generalized edema. There was no consolidation. The pulmonary arteries, including the trunk, were patent and showed no congenital anomalies. There was no atherosclerosis or dilatation. However, because of the peculiar position of the lungs and heart, there was some distortion of the main pulmonary artery. The aorta showed a minimum of sclerosis. It followed the tortuous course of the spine and showed no changes in circumference.

The liver weighed 800 Gm. It was yellowish brown, and its consistency was normal. On section, it showed the mottled nutmeg appearance of passive congestion. The spleen weighed 50 Gm., and the kidneys, 150 Gm. each. They appeared normal except for evidence of passive congestion. The pelvic organs appeared normal. No enlarged lymph nodes were found. The brain and spinal cord were not removed.

Microscopic Examination.—Sections of the liver showed severe chronic passive congestion. The lungs showed edema, with mild emphysema. There was no evidence of any pulmonary arteriosclerosis. The remaining organs appeared normal.

DISCUSSION

The mechanism by which the right-sided cardiac hypertrophy and failure are brought about in chest deformities is not difficult to understand. The deformed thorax is small and the diaphragm is high. Since the thoracic deformity is usually established in childhood, the chest does not develop in proportion to the rest of the body. In cases of severe kyphoscoliosis, marked distortion and displacement of the larger pulmonary vessels exists. As a result, the volume of the lungs and the vital capacity are greatly reduced. Emphysema is frequently a compensatory phenomenon. The pulmonary artery may become dilated. The pressure within the pulmonary circulation becomes elevated. A greater burden is placed on the right side of the heart. This eventually leads to right ventricular hypertrophy, which may be followed by dilatation and cardiac insufficiency. Cardiac failure is usually a gradual process, extending over a long period of time. Boas[4] calls attention to the difficulty of interpreting physical signs in these cases because of the great deformity of the chest. It is often impossible to ascertain whether or not cardiac hypertrophy is present, and murmurs are difficult to recognize. Electrocardiograms usually reveal right ventricular hypertrophy. Roentgenologic studies show enlargement or dilatation of the pulmonary artery and conus, without evidence of any significant hypertrophy of the left ventricle. Once the signs of myocardial insufficiency appear, as in other cases of cor pulmonale, the prognosis is extremely poor, for these patients do not respond well to digitalization. Chapman, and associates,[7] found that the average age at death of 79 such patients was 30 years. The only hope lies in early treatment of spinal deformities.

SUMMARY

The case of a 27-year-old woman who suffered from severe kyphoscoliosis since childhood is reported. Death was caused by right-sided cardiac hypertrophy and insufficiency secondary to the chest deformity. Attention is called to the part severe chest deformities may play in the development of right ventricular hypertrophy and failure.

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JUVENILE ELONGATION OF THE AORTA

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CASE REPORT

H. C. C., a Chinese, aged 12 years, was seen in the United Hospital in January, 1940. He gave a history of dislocation of the right wrist as a result of a fall from a height of about 12 feet, three years earlier. Discharging sinuses had been present for about two years. The clinical impression was traumatic dislocation of the right wrist, with chronic osteomyelitis. Routine fluoroscopic examination of the chest revealed normal lungs and diaphragm. The unusual changes that caught the eye were a markedly elongated and tortuous aorta, with its upper end extending well into the left upper lung field, and prominence of both ventricles, especially the left. Pulsations appeared normal. The retrocardiac space was clear. A roentgeno-

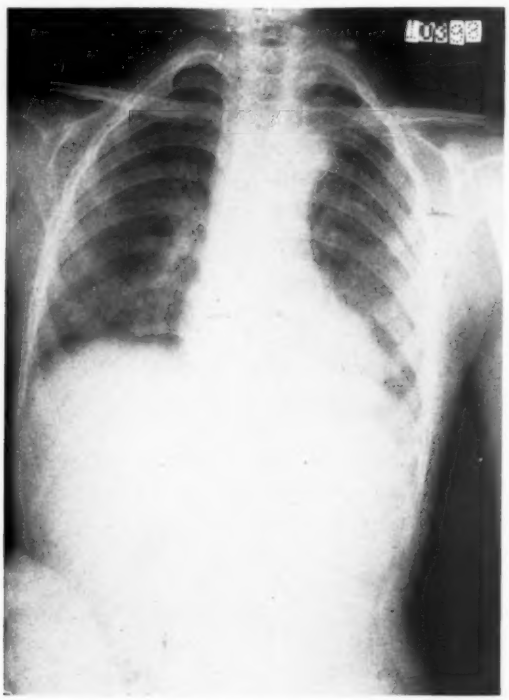

Fig. 1.

gram taken with a target-film distance of 250 cm. (Fig. 1) confirmed the fluoroscopic observations. The heart appeared slightly wider and larger than normal. The general outline of the heart was somewhat sabot-shaped, with moderate rounding of the left border and less of the right. The aorta appeared moderately elongated, and had a rather tortuous knob, the superior border of which corresponded

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in level to the fourth thoracic vertebra. The cardiothoracic ratio was 0.54, and the width of the aortic shadow was 5.4 cm. The ribs showed no abnormality.

Because of the striking roentgenologic abnormalitis, attention was paid to other systems, particularly the cardiovascular. The patient, however, gave no history of cardiovascular disease. There was no cyanosis, edema, or clubbed fingers. The blood pressure was 110/60. The urine and stool were normal. The hemoglobin was 85 per cent, and the leucocyte count, 9,800. The differential count was normal. There were no stigmata of congenital syphilis. Unfortunately no electrocardiogram was available at that time. Dr. C. Wu made a detailed examination of the cardiovascular system. Auscultation revealed hyperdynamic heart sounds, with a Grade I systolic murmur at the aortic area; the first sound at the apex seemed to be reduplicated (? normal third sound). There was nothing else remarkable.

In the absence of any other clinical or laboratory abnormalities, it was difficult to account for the roentgenographic appearance of the aorta and heart. It was therefore felt that several possibilities should be considered, among which were (1) a congenital anomaly, (2) juvenile arteriosclerosis (clinically latent, perhaps as a result of toxic absorption from the chronic osteomyelitis of the right wrist), and (3) juvenile hypertension.

DISCUSSION

A search through the recent literature showed no similar case. No comparative information could be gleaned from roentgenologic sources. There was but scant mention of the normal aorta and its variations in childhood in roentgenologic texts, including Roesler's,[1] Polevski's,[2] and Vaquez and Bordet's,[3] or in textbooks of cardiology, such as White's.[4] Pathologic or congenital enlargement or elongation was not described. Some textbooks of medicine and cardiology briefly mentioned the occurrence of arteriosclerosis or of hypertension in childhood, but said nothing about any roentgenologic changes. Occasional reports of juvenile arteriosclerosis have appeared in the literature. Guild, Kindell, and Gibson[5] described two such cases in detail, in one of which there was mild involvement of the aorta, but no roentgenograms were shown. The writer therefore feels that the roentgenographic changes in the case reported here are unique, in spite of uncertainty concerning the causative factor. It appears that thorough studies of the roentgenologic appearance of the normal aorta and its variations in childhood, not excluding pathologic changes, are indicated.

SUMMARY

Marked elongation and tortuosity of the aorta, with some hypertrophy of both ventricles of the heart, particularly the left (but with no frank clinical evidence of disease of the cardiovascular or renal system), were discovered roentgenologically in the case of a boy, 12 years old, who was suffering from traumatic dislocation of the right wrist complicated by chronic osteomyelitis. It was felt that the unusual appearance of the aorta and heart might be explained by (1) a congenital abnormality, or (2) some juvenile degenerative or hypertrophic change

brought about by unknown factors (toxic?) which were perhaps related to the chronic infection of the right wrist.

The writer is indebted to Dr. S. H. Wang for his invaluable help in the preparation of this article.

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TWO CASES OF DISSECTING ANEURYSM OF THE AORTA, WITH ANTE-MORTEM DIAGNOSIS

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In 1933, Shennan collected from the literature three hundred seventeen cases of dissecting aneurysm of the aorta, in six of which the diagnosis had been made antemortem. Since that time there have been numerous reports, indicating an increasing interest in, and more frequent recognition of, this morbid state. One hundred fifty-one cases have been reported in the American literature since Shennan's review. Of these, an ante-mortem diagnosis was made in thirty-four. To this group we are adding two cases in which the diagnosis was made clinically.

Two hundred eighty-three cases of hypertension of various kinds have been seen in the Lilly Laboratory for Clinical Research at the Indianapolis City Hospital during the past four years. Two patients in this series developed dissecting aneurysm of the aorta, which is an incidence of less than one per cent.

Of the one hundred fifty-one cases in the literature, hypertension was known to be present in one hundred seven. Of forty-two patients who had had no previous blood pressure recordings, twenty-three were found to have hypertension, and the other nineteen were in a state of shock. Two patients had a normal arterial pressure before and after the onset of symptoms. Since dissecting aneurysm is occasionally a complication of hypertension, and is associated with it in the majority of cases, we are presenting the features which characterize this condition. Coronary disease, with subsequent occlusion, is frequently observed in hypertensives. Yet these two conditions, although they present similar symptoms, have a different prognosis, i.e., some patients with coronary occlusion recover.

CASE REPORTS

M. S., a white man, aged 49, a manufacturer, complained of nervousness, headaches, nausea, blurred vision, and substernal pain. Ten years prior to admission to the Lilly Clinic it was found that his arterial pressure was slightly elevated. In May, 1939, he had a sudden, severe pain in the lower lumbar region which, he said, felt "as if someone hit me with a baseball bat." The pain radiated to the groin and inner aspects of the thighs. At that time he was in another hospital for two weeks. No abnormalities were noted, and the pain did not recur. In December, 1939, the patient had a cerebral hemorrhage which resulted in a disturbance of speech and mild facial paralysis. From that time he complained of headaches, nervousness, and palpitation. Three months later his physician made a diagnosis of malignant

From Lilly Laboratory for Clinical Research, Indianapolis City Hospital.
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hypertension because of papilledema, retinal hemorrhages and exudates, and a marked elevation of blood pressure. At three o'clock on the morning of admission the patient had a severe substernal pain which required a grain of morphine for relief. In the opinion of the referring physician, the patient had coronary occlusion.

Physical examination showed papilledema and moderate constriction and sclerosis of the retinal arterioles, with hemorrhages and exudates. The tongue deviated to the left and the mouth was drawn to the right. There was moderate cardiac enlargement, with a loud systolic murmur at the apex; intermittent gallop rhythm was present. The blood pressure was as follows: left arm, 222/158; right arm, 218/152;

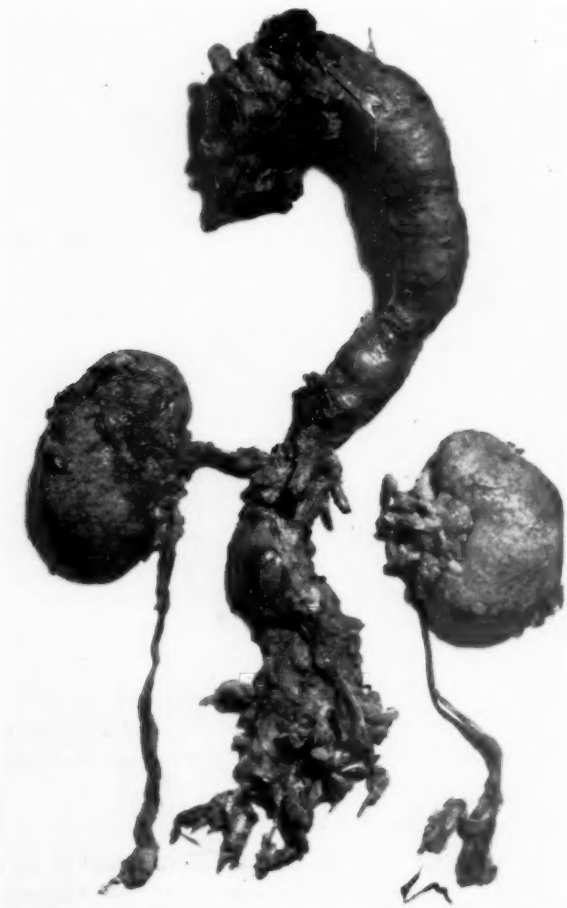

Fig. 1.—M. S., autopsy specimens, showing aorta, renal vessels, kidneys, and ureters.

left leg, 268/194; and right leg, 292/214. All of the reflexes were hyperactive. During the patient's hospital stay of twenty-eight days, the erythrocyte count fell from 4.9 to 4.0 million, and the hemoglobin from 100 per cent to 65.4 per cent. A leucocytosis of 14,000 persisted. The urea clearance averaged 35 per cent of normal, and the blood urea nitrogen ranged from 13.9 mg. per cent to 18.5 mg. per cent. Hematuria was present constantly. The transverse cardiac diameter was +27 per cent (Ungerleider-Clarke). A roentgenogram of the chest showed

some widening of the aorta. The electrocardiogram showed inversion of the T wave in all leads, and a biphasic QRS in Leads II and IV. The impression from the electrocardiogram was that coronary occlusion might have occurred. There was gradual improvement, as indicated by later electrocardiographic changes.

Because of the constant substernal and epigastric pain, without fall in blood pressure, a diagnosis of malignant hypertension and dissecting aneurysm of the aorta was made. In order to confirm the diagnosis, a fluoroscopic examination of the chest was done, and this revealed generalized widening of the aorta. The aorta cast an unusually dense shadow.

During his hospital stay the patient complained almost constantly of pain in the back of the neck, behind the sternum, and in the epigastrium. On the twentieth day a to-and-fro friction rub was heard along the left border of the sternum. The pain increased in severity and his pulse became irregular. There was a moderate febrile reaction and the leucocytosis persisted, but no changes were recorded in the electrocardiogram. Three days later the pain became almost unbearable and continued unabated. There were marked abdominal distention and occasional projectile vomiting. Persistent gallop rhythm developed, and the heart sounds were sharp and snapping. The patient died unexpectedly, while asleep, on the twenty-eighth day after the onset of pain.

Post-mortem examination by Dr. H. C. Thornton showed that the left pleural sac contained about 1000 c.c. of serous fluid. The lung was collapsed and the mediastinum was pushed to the left by a large blood clot in the mediastinum. The clot weighed 2128 Gm. The heart weighed 528 Gm., and the myocardium was pale and flabby. There were moderate atherosclerosis of the aorta and marked sclerosis of the coronary arteries. No occlusion of the coronary vessels was noted.

There was a ragged opening in the aorta, 2.5 cm. in diameter, on the superior and lateral aspect, about 2 cm. distal to the left subclavian artery. A dissecting aneurysm involved the distal portion of the arch, all of the thoracic portion of the aorta, and the upper portion of the abdominal aorta as far as the superior mesenteric artery, down which it extended a short distance. In the thoracic aorta the aneurysm measured 2 cm. in thickness and extended 3 cm. around the wall. The lumen was compressed by the aneurysm, which was filled with a fresh thrombus. Another partially healed dissecting aneurysm involved the lower abdominal aorta and the left common iliac artery. An opening 5 mm. in diameter, with smooth edges, was found on the anterior wall of the aorta about 3 cm. proximal to the bifurcation. This opening led into the aneurysm, which extended upward from the opening about 5 cm., and downward to the bifurcation and along the left common iliac artery. In the lower aorta the aneurysm was 2.5 cm. in diameter, and the upper portion was occupied by an old, pale, firm, apparently organized thrombus. There was a third dissecting aneurysm in the left renal artery which partially occluded the lumen of the vessel.

E. F., a white man, aged 54, a salesman, was admitted to the Lilly Clinic Sept. 8, 1939, complaining of severe abdominal, interscapular, and precordial pain of ten days' duration. The patient had first noticed headaches, nocturia, and vertigo five years before, at which time his blood pressure was 200/120. Two years later, roentgenologic examination revealed enlargement of the heart, with widening of the aortic arch and tortuosity of the descending aorta. The electrocardiogram was normal. The vertigo, nocturia, and headaches persisted, but no physical abnormalities were noted except the elevation in blood pressure. Symptomatic improvement occurred on thiocyanate therapy. Two months before admission he had severe interscapular and abdominal pain which lasted one-half hour. A month later he had a severe, stabbing pain in the right, anterior part of the chest.

The present illness had begun suddenly while the patient was driving a car. He had a sharp pain between the scapulae, with abdominal cramps. When he tried to

stop the car he could not move his feet and legs. He pulled himself out of the car because he wanted to urinate and defecate, but was unable to do either. After lying by the roadside for an hour he managed to drive to a physician's office. The pain was temporarily relieved by one-half grain of morphine.

Physical examination on admission showed severe constriction and moderate sclerosis of the retinal arterioles. There was increased precordial activity, and a roughened, accentuated first sound was heard in the mitral area. The blood pressure was 244/144 in the left arm. Marked rigidity of the abdominal wall was present, and there was a Babinski reflex on both sides. The erythrocyte count was 3.86 million, and the leucocyte count gradually increased from 9,500 to 14,000. The blood urea nitrogen was 29 mg. per cent, and the urea clearance was 53.8 per cent of normal. The electrocardiogram showed left axis deviation.

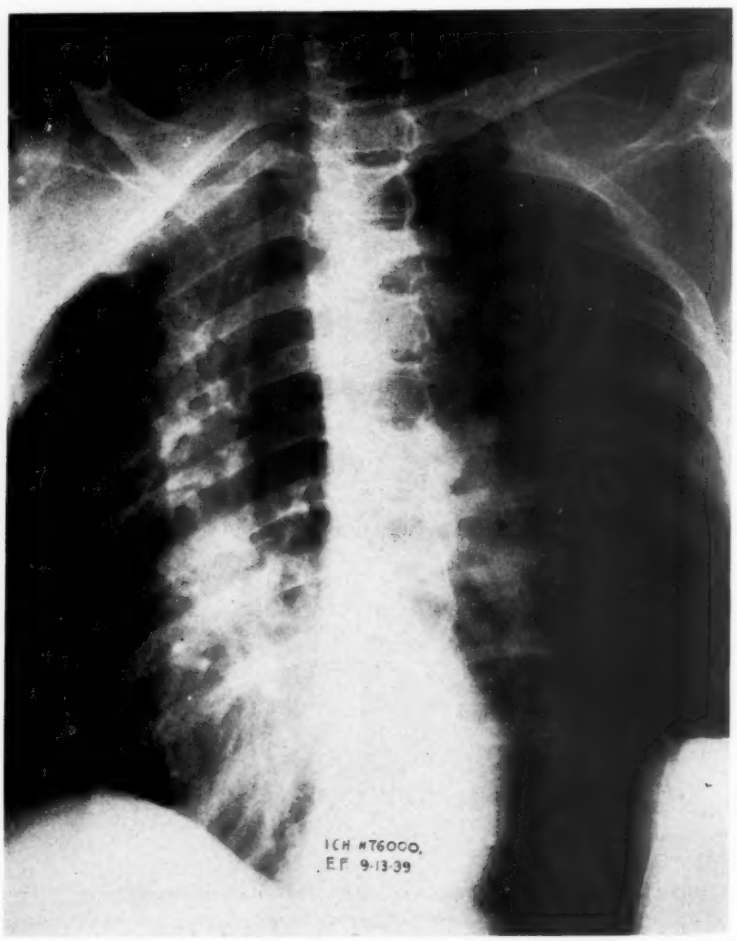

Fig. 2.—E. F., Sept. 13, 1939. Roentgenogram showing widening and increased density of the aortic shadow.

Moderate doses of morphine failed to relieve the patient's pain, and, on the fifth day of his hospital stay, hiccough became a distressing symptom. In order to differentiate dissecting aneurysm of the aorta from diaphragmatic irritation of unknown origin, fluoroscopic examination was done. There was widening of the

aortic arch and the descending aorta. About 2 cm. above the diaphragm there was a marked out-pouching of the aortic wall to the left. Later on the same day the patient died suddenly while talking with the resident physician. The clinical diagnosis was essential hypertension and rupture of a dissecting aneurysm of the aorta.

At post-mortem examination the left thoracic cavity was completely filled with freshly clotted blood. The left lung was partially collapsed. The transverse diameter of the pericardium measured 15 cm. The ascending aorta was relatively normal. Between the intima and muscularis of the descending aorta there was an organized thrombus which measured 2 cm. in thickness and 11 cm. in length. The thrombus completely encircled the aorta and extended downward to about 2 cm. above the diaphragm, i.e., to the point of rupture on the lateral aspect of the vessel. The muscularis was friable and necrotic. The intima was covered with many atheromatous plaques, and, at two points in the first part of the descending aorta, there were necrotic areas. In the center of one of these there was a communication between the lumen of the vessel and the aneurysmal sac. The dissection continued along the arch of the aorta to within a few centimeters of the aortic valve. The heart weighed 480 grams; the hypertrophy was, for the most part, of the left ventricle. The coronary arteries were moderately sclerosed. Another dissecting aneurysm was found in the pancreatic artery at the point of its entrance into the gland.

The important microscopic abnormality in the aorta was thickening of the adventitia with many fibroblasts. The adventitia had a loose, edematous appearance, and contained numerous polymorphonuclear leucocytes and lymphocytes. The majority of the vasa vasorum were thrombosed. There was a large thrombus in the media, the inner portion of which showed marked degeneration and necrosis.

DISCUSSION

We wish to stress the points in a typical case of dissecting aneurysm which we feel are important in making a diagnosis.

If a patient is known to have high blood pressure it is important that frequent readings be recorded. It is a rule in this clinic that the arterial pressure of each patient must be taken in each extremity during the course of his physical examination at the time of admission. If there is any abnormality in the readings, they are repeated frequently. Otherwise, measurement twice daily in the left arm is the rule. A persistently high blood pressure with the symptoms of coronary occlusion should cause one to question the latter diagnosis.

A continued, agonizing pain, radiating from the area of dissection of the aorta, is the most outstanding symptom. The examining physician may discredit the patient's complaints because of the improbability that comparatively good health could be followed so quickly by desperate illness. Pain, with temporary paralysis of the extremities, is usually caused by actual dissection of the main artery, thrombosis of a vein, or embolism. The pain of coronary occlusion seldom radiates below the sacrum, but in dissecting aneurysm it commonly radiates to the legs. Associated with the pain, coldness and diminution or absence of the pulsations of the arteries are observed. The latter may be transient.

There is a peculiar grayish cyanosis which accompanies the patient's appearance of anxiety. It is not the pallor of shock or the cyanosis of respiratory distress, and it is not relieved by the administration of oxygen.

The temperature may be subnormal if the patient is in shock, or moderately elevated. There is usually an increase in the leucocyte count. Of the one hundred fifty-one cases reviewed, in forty-five there was a leucocytosis of 9,500 to 34,000; in one hundred three no count was recorded; and, in three, the count was normal. The importance of the progressive anemia which follows extensive bleeding into the aortic wall has not previously been stressed. In one hundred thirty-one of the cases reviewed, no erythrocyte count was recorded; sixteen patients were known to have progressive anemia, and four had no anemia.

Taking a roentgenogram of the chest is a routine procedure in most clinics. Certainly any patient with hypertension should have a teleoroentgenogram. If the cardiac, aortic, or mediastinal shadow is abnormal, subsequent roentgenograms may disclose progressive enlargement. Fluoroscopic examination is usually an aid in the diagnosis of aneurysm. Thirty-one of the one hundred fifty-one patients had roentgenologic abnormalities suggestive of dissecting aortic aneurysm; one hundred fifteen had no roentgenologic examination; and only five had normal shadows.

What the electrocardiogram will show depends upon the degree of myocardial damage, the site of the dissection, and the state of the coronary arteries. Since this condition occurs most frequently in hypertensive patients, left axis deviation is common. If there is much coronary sclerosis there may be changes in the T waves and the S-T segment. Should the dissection involve the coronary ostia or the arteries themselves, there may be changes which are typical of myocardial infarction. The point is that there is no typical electrocardiographic pattern in this disease.

SUMMARY

In a series of two hundred eighty-three patients with hypertension, two developed dissecting aneurysm of the aorta. Although these two patients had signs and symptoms of coronary thrombosis, this diagnosis was ruled out by several significant features. In both cases the pain occurred first in the chest and then radiated to the shoulders, back, abdomen, or extremities. It was so agonizing that large doses of morphine failed to give relief. The blood pressure remained elevated, and, in the first case, it was not the same in the upper and lower extremities and was higher in the right leg than in the left. Mild fever, moderate leucocytosis, and anemia were present. Roentgenographic and fluoroscopic examination of the chest showed widening of the aorta and mediastinum. Post-mortem examination confirmed the diagnosis of dissecting aneurysm of the aorta in both cases.

We appreciate the assistance of Dr. Helen L. Crawford, of the Department of Roentgenology.

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Abstracts and Reviews

Selected Abstracts

Tocantins, L. M.: Loss of Prothrombin Activity in Plasma Exposed to Air Currents. Proc. Soc. Exper. Biol. & Med. 49: 251, 1942.

Exposure of citrated or oxalated plasma to an air current is followed by a rapid diminution in its prothrombin activity probably due to rapid evaporation and loss of CO_2. Addition of CO_2, even by saturating the plasma with expired air, restores prothrombin activity to its initial level, while bubbling oxygen through the plasma has no effect. Changes in CO_2 content of the blood may explain the difference in prothrombin activity of the blood entering and leaving the lungs. Asphyxia or hyperventilation may be expected to produce significant fluctuations in the prothrombin activity of the blood.

WILLIAMS.

Wakim, K. G.: Effect of Stimulation of Autonomic Nerves on Intrahepatic Circulation of Blood in Intact Animal. Proc. Soc. Exper. Biol. & Med. 49: 307, 1942.

The effect of stimulation of the sympathetic and parasympathetic nerves of anesthetized frogs and albino rats on the intrahepatic vessels was observed by transillumination of the intact liver. Stimulation of the nerve plexuses in the porta hepatis and around the hepatic artery of frogs by weak or strong tetanizing current caused constriction of the active sinusoids, some of which contracted to disappearance. Constriction appeared within two seconds after the beginning of stimulation and lasted for four to five seconds after discontinuance of stimulation. Immediately after pithing there was a marked reduction in the number of active sinusoids. This inactivity resulted in either a constrictor effect, leading to very narrow sinusoids containing hardly any corpuscles, or more commonly in stasis with the sinusoids packed full of corpuscles lying motionless in their lumina. After about fifteen minutes circulation began to recover in the inactive lobules, but more inactive sinusoids were seen than in an intact anesthetized frog. Stimulation of the plexus of nerves in the porta hepatis and around the hepatic artery in rats produced moderate blanching and constriction of the sinusoids. There was a latent period of about five seconds, and the sinusoids resumed activity about ten seconds after cessation of the stimulus. Arterial sinusoids were constricted more markedly than the venous ones. Arteriovenous anastomoses constricted to disappearance. Stimulation of both vagus nerves did not cause any perceptible changes in the circulation of the liver.

WILLIAMS.

Helmer, O. M., and Page, I. H.: Formation of Angiotonin-like Pressor Substance From Action of Crystalline Pepsin on Renin-Activator. Proc. Soc. Exper. Biol. & Med. 49: 389, 1942.

The observation by Croxatto and Croxatto that commercial pepsin at pH 2.0 reacts with renin-activator to form a pressor substance with properties similar to those of angiotonin was confirmed. Crystalline pepsin was found to react in the

same manner. The reaction between pepsin and renin-activator is halted at pH 6.5. The effect of pH on this reaction is quite different from the effect of pH on the formation of angiotonin from renin and renin-activator; angiotonin is formed abundantly at pH 6.5 to 7.0 but not at all at pH 2.0 to 4.0.

WILLIAMS.

Huidobro, F., and Braun-Menendez, E.: The Secretion of Renin by the Intact Kidney. Am. J. Physiol. 137: 47, 1942.

Profound lowering of the blood pressure by hemorrhage (4 per cent of body weight) or shock causes the liberation of renin by the intact kidney of normal anesthetized dogs. Renin can be detected in the systemic blood of these dogs. Renin could not be detected in the blood of nephrectomized dogs after hemorrhage or in normal dogs intoxicated with KCN or subjected to respiration of mixtures poor in oxygen. After short periods of 4 to 11 minutes of profound arterial hypotension renin could be detected in the systemic blood of normal dogs.

The inference is drawn that the kidney participates in the regulation of arterial blood pressure. When the blood pressure decreases the normal kidney secretes renin which through the formation of hypertensin tends to the restoration of normal blood pressure. Renin appears to be a substance which the body uses to maintain homeostasis.

AUTHORS.

Goss, C. M.: The Physiology of the Embryonic Mammalian Heart Before Circulation. Am. J. Physiol. 137: 146, 1942.

The following points concerning the fundamental or intrinsic powers of the myocardium have been made in the author's observation of early embryonic hearts: First, the power of spontaneous rhythmic contraction is possessed by each of the chambers and they have their own intrinsic rates. Second, the contraction of the myocardium progresses by a wave from one end of the chamber to the other. Third, the atrioventricular interval which makes coordination of the whole heart possible appears along with atrial contraction itself. Fourth, the spontaneous rhythm of the ventricle is inhibited by the atrium. Fifth, mechanical work, pumping the blood, begins after the preparatory development outlined above.

AUTHOR.

Cope, O., Brenizer, A. G., Jr., and Polderman, H.: Capillary Permeability and the Adrenal Cortex Studies of Cervical Lymph in the Adrenalectomized dog. Am. J. Physiol. 137: 69, 1942.

Lymph was collected from the cervical trunk of normal and adrenalectomized dogs under local anesthesia. The protein content of the lymph of the normal animals averaged 2.8 grams/100 c.c., and of the adrenalectomized 4.3 grams. The increase above normal was as great in the dogs in moderate as in severe insufficiency and was not merely an accompaniment of a moribund state. The finding offers direct evidence of an increase in capillary permeability in one region of the dog in adrenal insufficiency.

The significance of this protein increase in lymph to the osmotic equilibrium between blood plasma and extracellular fluid is discussed.

The flow of lymph was in general, but not consistently, reduced in insufficiency. The extracellular fluid volume, measured by means of thiocyanate, was increased as well as decreased.

AUTHORS.

Pappenheimer, J. R., and Maes, J. P.: A Quantitative Measure of the Vasomotor Tone in the Hindlimb Muscles of the Dog. Am. J. Physiol. **137**: 187, 1942.

The hindlimb muscles of anesthetized dogs were perfused with defibrinated blood at constant pressure from a pump-lung circulation. The sciatic nerve to the muscles was left intact. At intervals the nerve was reversibly blocked by cooling and the changes of blood flow measured at different perfusion pressures. The blood perfusion could be interrupted by periods of Ringer perfusion.

With the blood vessels unconstricted (nerve blocked) the relations between the pressure and the flow of blood or of Ringer's solution were similar to those found by Whittaker and Winton (1933) in the isolated hindlimb.

During vasoconstriction the following changes occur in the pressure-flow curves: a. The pressure at which the pressure-flow curve of blood becomes approximately linear is increased. Below this pressure the slope diminishes and the curve approaches the origin. The extrapolated intercept of the linear part of the curve increases with increasing vasoconstriction. b. The Ringer pressure-flow curve is a straight line which intercepts the pressure axis at or near the origin. Its slope is diminished by vasoconstriction but its intercept is unaffected.

The apparent relative viscosity of the blood (ratio of Ringer flow to blood flow at constant pressure) is increased during vasoconstriction. The amount of increase varies in different muscles and in the same muscles with the degree of vasoconstriction and with the pressure. Extreme values for blood of normal corpuscular concentration are 2 to 8. At normal pressures the change of apparent viscosity accounts for about ¼ of the total change of resistance to blood flow caused by vasoconstriction.

For any constant degree of vasoconstriction the ratio of the Ringer flows at constant pressure in the unconstricted and in the constricted blood vessels is approximately equal to the ratio of the slopes of the pressure-flow curves of blood in the unconstricted and in the constricted vessels, both slopes being measured over the linear parts of their characteristics.

The evidence suggests that this ratio is independent of the viscosity and is a measure of the change in the average dimensions of the blood vessels. In the innervated preparation it is proposed as a measure of the vasomotor tone. Its value has varied from 1.0 (no vasomotor tone) to about 3.5. Reasons are given for supposing that the measure is quantitatively comparable in the muscles of different experiments.

AUTHORS.

Heilig, R.: The Pathological Heart Conditions in Hookworm Disease and Their Causes. Indian M. Gaz. **77**: 257, 1942.

Sixty-five cases of uncomplicated severe hookworm anemia were selected among an unlimited material of ankylostomiasis, as it is found in Mysore, South India. The characteristic signs, which the heart presents in untreated cases, are bilateral dilatation, mitral configuration, a thumping first sound and a systolic murmur in the apical area, an accentuated pulmonary second sound and a harsh systolic murmur in the second left interspace different in character from that heard at the apex. On fluoroscopy an expansile pulsation of the heart contour is regularly seen; epigastric pulsation is frequently felt. The blood pressure is about 100-110 mm. Hg systolic and rarely more than 50-60 diastolic. The electrocardiogram always showed signs of a definite myocardial lesion such as a very low general voltage, depressed or downwards convex S-T junction and a flat or isoelectric T in all the leads. In fifty-nine (90 per cent) of these cases all the pathological signs elicited on percussion, auscultation, fluoroscopy and electrocardiography disappeared completely after four to six weeks of mere antianemic treatment with large doses of iron (Blaud's pills, gr. 90 per day) before deworming was per-

formed. In six cases, women all of them, the pathological heart condition deteriorated in all aspects in spite of perfectly satisfactory blood response to equally intensive antianemic treatment until the last hookworm was eliminated. Ten days to three weeks after complete deworming the same improvement of the heart condition was observed as it was seen in the other cases already before anthelminthic treatment was performed. These results point towards the existence of a hookworm toxin; the myocardial damage which is caused by its action could be overcompensated by improvement of the red blood picture in the majority of hookworm anemias, whereas a minority remained where its damaging influence continued independently of the blood condition, as long as more than three to five hookworms escaped destruction.

AUTHOR.

Moia, B., Inchauspe, L. H., Olmedo, R. C., and Battle, F. F.: The Electrocardiogram in Simultaneous Increase in Size of Both Ventricles. Rev. argent. de cardiol. **9**: 1, 1942.

The effect on the electrocardiogram of simultaneous enlargement of both ventricles was studied in 96 young patients in which rheumatic aortic insufficiency coexisted with mitral stenosis. None of these patients received digitalis, nor had auricular fibrillation or signs of active carditis or pericarditis. The nonexistence of other factors, especially coronary disease, was thus presupposed.

From these 96 patients 20 were selected for this study because of the absence in their electrocardiograms of the characteristic alterations of aortic insufficiency or mitral stenosis. A case of arterial hypertension with pulmonary sclerosis was added in which necropsy showed the absence of coronary alterations of the stenotic type.

The electrocardiograms of these patients, apart from the absence of axis deviation, showed in the standard leads and in precordial leads CF_1, CF_2 and CF_4 and in the sagittal derivations the following changes:

QRS.—Right axis deviation ($R_3 > R_2$) with absence of S_1; absence of definite axis deviation with S_3; triphasic complexes with positive initial deflection in L_3 or in L_3 and L_2, with sometimes very deep S_3.

ST segment.—Even in the absence of definite axis deviation the ST segment was depressed in only one (L_1) in two (L_2 and L_3) or in the three standard leads; depressed in L_1 and elevated in L_3 or elevated with a rectilinear stretch in L_3.

T wave.—High voltage in one or more leads and negative, disphasic or flat in L_3. The cases with alterations of the ST segment showed generally negativity or diphasism of T in L_1, or diphasism in L_1 and L_2 with flat T_3 or negativity in the three leads especially in L_2 and with a conformation very similar to the so-called "coronary T wave."

Deep inspiration did not modify these patterns. Precordial leads did not show any definite alterations. In some cases the sagittal lead showed in L_3 a clear left type, the concordant ST deviation changing into the opposite.

The cause of these alterations and their diagnostic significance is discussed and attention is drawn to the fact that in many cases they are very similar to those alterations which appear in the electrocardiogram in cases of myocardial damage (ischemia, infectious diseases, etc.) and pericarditis.

AUTHORS.

Goldburgh, H. L., Baer, S., and Lieber, M. M.: Acute Bacterial Endocarditis of the Tricuspid Valve. Am. J. M. Sc. **204**: 319, 1942.

In 26,007 necropsies there were 646 cases of acute bacterial endocarditis, an incidence of 2.5 per cent.

The mitral valve, singly, was most frequently involved (47.6 per cent) followed by the aortic valve, singly (25.4 per cent), mitral and aortic (18.7 per cent), and tricuspid, singly (3.1 per cent).

Lesions were limited to the tricuspid valve in 20 cases, an incidence of 3 per cent of acute bacterial endocarditis and 1 out of 1,300 autopsies.

Right-sided bacterial endocarditis occurred in 8.2 per cent of the cases.

Lesions involved the tricuspid valve alone in 9 of the 62 cases of pneumococcic bacterial endocarditis (14.5 per cent).

The lack of diagnostic auscultatory findings in acute bacterial endocarditis of the tricuspid valve is emphasized.

AUTHORS.

Gelfman, R., and Levine, S. A.: The Incidence of Acute and Subacute Bacterial Endocarditis in Congenital Heart Disease. Am. J. M. Sc. 204: 324, 1942.

The protocols of four Boston hospitals were reviewed to determine the incidence of acute and subacute bacterial endocarditis and endarteritis among congenital cardiac defects. Special attention was paid to sex, age at time of death, type of cardiac defect and superimposed rheumatic infection.

In 34,023 autopsies, 453 (1.3 per cent) contained significant congenital cardiac defects, 181 of which (40 per cent of the 453) were in patients over the age of 2 years.

Evidence of bacterial endocarditis was present in 6.5 per cent of the 453 cases and in 16.5 per cent of the 181 cases over 2 years of age.

The distribution of males and females was in a proportion of 3 to 2 in both the total group with cardiac defects and in those who showed infectious endocarditis.

Sixty per cent of the patients died before the age of 2 years. For the rest, no predominance was shown in any one age group. The highest incidence of bacterial endocarditis fell in the second and third decades.

Twenty-five (14 per cent) of the 181 hearts with congenital defects were further complicated by rheumatic infection. Congenital bicuspid aortic valve and interauricular septal defects were the most frequent underlying cardiac anomalies, and subacute bacterial endocarditis was present in 8 of these 25 rheumatic hearts.

The incidence of bacterial endocarditis in the most significant cardiac defects was as follows: interauricular septal defects, none; interventricular septal defects, 42 per cent of all and 57 per cent of the uncomplicated cases over 2 years of age; patent ductus arteriosus, 28.6 per cent of all and 20 per cent of the uncomplicated cases over 2 years of age; bicuspid valves, 17.4 per cent of all and 21 per cent of those over 2 years of age; tetralogy of Fallot, 12.5 per cent of all and 29 per cent of those over 2 years of age; pulmonic stenosis, 19 per cent of all and 29 per cent of those over 2 years of age.

AUTHORS.

Lev, M., and Strauss, S.: Stenosis of the Infundibulum. Arch. Int. Med. 70: 53, 1942.

A case of infundibular stenosis without transposition is presented from the clinical and the pathologic standpoint. The various types of infundibular stenosis are discussed, and the various theories concerning the pathogenesis of this anomaly are reviewed.

Infundibular stenosis is most frequently part of a tetralogy of Fallot and as such represents the result of an abnormality both in the absorption of the bulbus and in its incorporation into the right ventricle. When stenosis is present without transposition, the absorption of the bulbus must have proceeded normally but its final incorporation into the right ventricle must have been faulty.

AUTHORS.

Foster, D. B.: Association Between Convulsive Seizures and Rheumatic Heart Disease. Arch. Neurol. & Psychiat. 47: 254, 1942.

An attempt is made to determine whether rheumatic heart disease is of etiologic significance in the production of convulsive seizures. The study is based on a review of 2,153 patients presenting both conditions. It is concluded that the rheumatic state is of etiologic significance in the production of certain convulsive disorders. This is based on the following facts. The incidence of seizures in rheumatic patients is higher than in the general population. The age onset of seizures in patients with rheumatic heart disease is different from that of the general population. Acute rheumatic fever or Sydenham's chorea preceded the onset of convulsive manifestations in 58.6 per cent of 29 patients; in 34.4 per cent the relation was doubtful, and in 6.8 per cent the convulsive seizures preceded the acute rheumatic infection. A familial incidence of convulsive seizures or migraine appears in the cases of rheumatic heart disease with seizures six times as frequently as in cases of rheumatic heart disease without seizures.

Several mechanisms may be operative in the rheumatic state capable of producing seizures in predisposed patients: paroxysmal cardiac arrhythmia, cerebral passive congestion, delayed auriculoventricular conduction, with or without the superimposition of digitalis, cerebral infarction, and possibly others.

KERSHBAUM.

Hoffman, G. L., Jr., and Jeffers, W. A.: Rheumatic Heart Disease Complicating Pregnancy. A Study of 61 Fatalities. Am. J. M. Sc. 204: 157, 1942.

Sixty-one maternal deaths due to rheumatic heart disease in Philadelphia during the past decade have been studied in reference to their preventability, manner of death and certain factors influencing the deaths.

Analysis of the manner in which death occurred among the cases studied indicated that the fatalities due to this disease resulted principally from congestive heart failure following delivery at, or near term.

Of the factors influencing death, the most important one amenable to control was the cardiac status of the patient at the time of delivery. Since this is almost solely dependent upon prenatal care, a significant decrease in the number of maternal deaths due to rheumatic heart disease can only be attained through an improvement in this care.

AUTHORS.

Pearce, John Musser: Susceptibility of the Heart of the Rabbit to Specific Infection in Viral Diseases. Arch. Path. 34: 319, 1942.

The intratesticular inoculation of vaccine, pseudorabies, inflammatory fibroma, strain A fibroma and myxoma viruses into rabbits which had been prepared by a preceding intravenous injection of a solution of acacia was followed by the appearance of cardiac lesions in the majority of the animals. Cardiac lesions did not occur or were of minor intensity in animals which had not had a preceding intravenous injection of the solution of acacia. In this respect the action of these viruses in localizing in the heart is similar to that previously described for virus III.

The lesions, regardless of the specific etiologic agent, were situated predominantly in the myocardium, but the viruses which are more prone to engender necrosis and exudation, i.e., vaccine virus and the viruses of pseudorabies and inflammatory fibroma, occasionally produced inflammation of the auriculoventricular valves.

The reaction in the heart was as a rule typical of the agent causing it. Thus in the acute exudative lesion of pseudorabies the intranuclear inclusion bodies

were seen. The myxoma virus induced proliferation of the typical large myxomatous cells, and the fibroma virus that of the characteristic fibroblasts, in the interstices of the heart muscle. The vaccine and inflammatory fibroma viruses brought about a less specific picture of muscle necrosis and leukocytic exudation.

AUTHOR.

Herbut, Peter A., and Maisel, Albert L.: Secondary Tumors of the Heart. Arch. Path. **34**: 358, 1942.

Thirty-five cases of secondary cancer of the heart are presented. The salient pathologic and clinical features are described, and an attempt at correlation of the two is made. In none of the cases in this series was the cardiac metastasis diagnosed before death.

AUTHOR.

Bruger, M., and Rosenkrantz, J. A.: Arteriosclerosis and Hypothyroidism; Observations on Their Possible Interrelationship. J. Clin. Endocrinol. **2**: 176, 1942.

The possible relationship between arteriosclerosis and the activity of the thyroid gland was investigated in subjects 55 years of age or older. The basal metabolic rate was correlated with the presence or absence of arteriosclerosis according to clinical criteria. It was found that the incidence of hypometabolism is greater for those exhibiting arteriosclerosis than for those without arteriosclerotic manifestations.

KERSHBAUM.

Horn, Henry, Klemperer, Paul, and Steinberg, Morris F.: Vascular Phase of Chronic Diffuse Glomerulonephritis: A Clinicopathologic Study. Arch. Int. Med. **70**: 260, 1942.

A series of 49 consecutive cases of chronic diffuse glomerulonephritis was investigated, with especial attention focused on the character of the arterial changes in all viscera. An independent and thorough evaluation of the clinical data in these same cases was also made.

In accordance with the varied vascular pictures a division of the disease into a slowly progressive and an accelerated phase is proposed, 14 cases representing the former and 35 cases the latter.

The histologic vascular lesions peculiar to each group of cases are described in detail. The intimal fibrosis, elastosis of arteries and arteriolar hyalinization which were characteristic vascular alterations in the slowly progressive group were also observed in the other groups. A transitional group, in addition, exhibited cellular proliferation, foam cells and edema of the arterial intima, while the advanced accelerated group revealed an even more conspicuous cellular intimal proliferation of the arterial tree and, in addition, distinct necrosis of the arteriolar walls.

A correlation of the clinicopathologic features was then determined. In the majority of cases it was found that the intensity of the clinical picture usually paralleled the anatomic vascular changes.

Neuroretinitis, common in the transitional and the advanced accelerated group, was never observed in cases of the slowly progressive phase of the disease.

On the basis of this survey it is concluded that arterial alterations both in the transitional and in the advanced accelerated groups of cases of chronic diffuse glomerulonephritis represent the anatomic equivalents of the clinical picture which has been designated malignant hypertension. This has been shown to occur more frequently than hitherto suspected in chronic diffuse glomerulonephritis.

In view of the constancy of severe hypertension in a miscellaneous group of diseases in which accelerated arterial changes are present, this factor is considered a potent etiologic force in their production. Whether hypertension is the basic determinant for the appearance of the vascular lesion or is itself mediated through the liberation of a toxic vasopressor substance is beyond the scope of this presentation.

The tempo of the clinical course in instances of chronic diffuse glomerulonephritis may be influenced not only by the exacerbation of the inflammatory process but by the height of the blood pressure.

The occurrence of severe hypertension and neuroretinopathy in disease entities of varied pathogenetic background vitiates the belief that these criteria may be of differential diagnostic import.

The vascular lesions once established contribute importantly to the advancement of the renal process and the intensification of the clinical picture.

AUTHORS.

Shure, Norman M.: Pyelonephritis and Hypertension: A Study of Their Relation in 11,898 Necropsies. Arch. Int. Med. 70: 284, 1942.

The incidence of hypertension in patients with pyelonephritis was studied from 11,898 autopsies performed in a ten-year period. In these the incidence was 44.4 per cent as compared to 34.9 per cent in a control group selected at random. In an analysis, however, this greater incidence apparently occurred in patients with bilateral pyelonephritis, especially in the male sex, and was most marked in men over 40. The relative absence of high blood pressure in patients with unilateral pyelonephritis was striking. The incidence of hypertension increased with the age of the patient and was parallel to the incidence of marked renal vascular damage. In small groups of patients with polycystic kidney, horseshoe kidney and uncomplicated nephrolithiasis the incidence of hypertension was 46.15, 64.7 and 53.25 per cent respectively.

AUTHOR.

Bellis, C. J.: The Portal Venous Pressure in Man. Proc. Soc. Exper. Biol. & Med. 50: 258, 1942.

The portal venous pressure was determined at laparotomy by inserting a needle, which was attached to a manometer filled with saline, into an omental vein; at the same time, with a similar apparatus, the ankle venous pressure was determined. In sixteen cases the average normal portal pressure was 10 cm. saline higher than the average normal ankle venous pressure. Normal portal pressures ranged between 14 and 22 cm. saline and normal ankle pressures ranged between 5 and 12 cm. saline. In a case of advanced portal cirrhosis with ascites, the portal venous pressure was 40 cm. saline, the ankle venous pressure 8 cm. saline, a difference of 32 cm. saline.

WILLIAMS.

Bean, W.: A Note on the Development of Cutaneous Arterial "Spiders" and Palmar Erythema in Persons With Liver Disease and Their Development Following the Administration of Estrogens. Am. J. M. Sc. 204: 251, 1942.

The development of cutaneous arterial "spiders" in 2 of 3 chronic alcohol addicts and palmar erythema in 1, following therapy with potent estrogens suggests that these stigmata of liver disease, pregnancy and deficiency diseases may result from abnormal metabolism of the 17-ketosteroid hormones.

AUTHOR.

Schlossmann, Nathaniel Charles: Fibrinoid Necrosis in Arteriosclerosis. Arch. Path. **34**: 365, 1942.

Homogeneous masses exhibiting the tinctorial behavior of fibrin and located within and on the arteriosclerotic plaques of the aorta and the peripheral vessels were analyzed in an attempt to establish their morphogenesis.

Fibrinoid substance could be clearly differentiated from fibrin by controlled tryptic digestion.

Evidence is submitted to establish the fibrinoid substance in arteriosclerotic vessels as partially necrotic collagen.

AUTHOR.

Mendlowitz, M.: The Digital Blood Flow, Arterial Pressure, and Vascular Resistance in Arterial Hypertension and in Coronary Thrombosis. J. Clin. Investigation **21**: 539, 1942.

Methods for calculating the digital blood flow from calorimetric observations have been modified and a method developed for calculating digital vascular resistance.

After vasodilatation produced by warming the body, normal digital blood pressure, blood flow, and vascular resistance were found in patients with neurogenic elevations of blood pressure. A consistent increase in digital vascular resistance and a normal digital blood flow were demonstrated in established essential or renal hypertension. In acute and in malignant hypertension, the digital blood flow may be decreased, and the vascular resistance increased out of proportion to the elevation in blood pressure.

Decrease in digital blood flow and blood pressure, and unchanged vascular resistance were demonstrated in cases of acute coronary occlusion, whether the antecedent blood pressure was normal or elevated.

AUTHOR.

Mendlowitz, M.: The Digital Circulation in Peripheral Vascular Diseases. J. Clin. Investigation **21**: 547, 1942.

The digital circulation was studied in Raynaud's syndrome, scleroderma, and thromboangiitis obliterans.

In Raynaud's disease and in scleroderma, the digital blood flow is usually decreased and the digital vascular resistance increased. In thromboangiitis obliterans, the digital blood flow is decreased because of a decrease in digital arterial blood pressure, the digital vascular resistance remaining comparatively unchanged.

Study of the digital circulation may be useful as an aid in diagnosis and prognosis, and as an index of the effect of therapy in peripheral vascular diseases involving the upper extremities.

AUTHORS.

Chipps, H. D.: Aneurysm of the Coronary Artery. Am. J. M. Sc. **204**: 246, 1942.

A case of mycotic embolic aneurysm of the anterior descending branch of the left coronary artery is presented. A review of the literature reveals 45 cases of coronary aneurysm and 9 of aneurysm of mycotic embolic origin. In this instance the source of embolism was a vegetative endocarditis of mitral and aortic valves due to the Strep. viridans. Impaction of the infected embolus in the coronary lumen caused not only the development of aneurysm but also coronary occlusion with infarction of the myocardium. The reasons for the rarity of mycotic embolic aneurysms of the coronary arteries are briefly discussed.

AUTHOR.

Gunther, L., Strauss, L., Henstell, H. H., and Engelberg, H.: Intramuscular Pressure. III. The Action of Various Drugs on Patients With Normal Intramuscular and Venous Pressure. Am. J. M. Sc. 204: 387, 1942.

Observations on the action of various drugs on intramuscular and venous pressures are shown in normal individuals. The drugs which are mainly pressor in action do not alter intramuscular pressure, whereas inhalations of CO_2 the tetanic state, and particularly the administration of coramine intravenously definitely raise the level of intramuscular pressure. An increase in intramuscular pressure is accompanied by an increase in venous pressure, whereas the reverse was not observed.

AUTHORS.

Gunther, L., Henstell, H. H., Strauss, L., and Engelberg, H.: Intramuscular Pressure. IV. The Venopressor Mechanism During the Course of Surgical Procedures. Am. J. M. Sc. 204: 394, 1942.

After 50 minutes of continuous surgery a drop in intramuscular pressure may precede the fall in venous pressure. In half the instances the low level of venous pressure coincided with the initial drop in intramuscular pressure.

When the intramuscular pressure falls and remains low for 50 minutes or longer, a further decrease in venous pressure occurs which reaches its maximum low point concomitantly with the maximum drop in intramuscular pressure.

Intramuscular pressure fell 5 minutes before the shocklike state began and the venous pressure with its full appearance 20 minutes later during a pericardial thoracentesis.

Further evidence is presented which supports Henderson's postulate in that: (a) intramuscular pressure first fails in shocklike states, and (b) with the failure of intramuscular pressure appears a failure in the maintenance of venous pressure and flow.

AUTHORS.

Lands, A. M., and Johnson, W.: Distribution of Body Water Following Hemorrhage. Proc. Soc. Exper. Biol. & Med. 49: 123, 1942.

The source of the water which dilutes circulating blood following hemorrhage was investigated by determining changes in the volume of cellular and extracellular water by comparing the volume of sulfocyanide available water both of the whole animal and of some of its organs after hemorrhage with the values obtained from normal animals. Thirty to sixty minutes after injecting sodium sulfocyanide in anesthetized cats a sample of blood was removed for analyses. Fifteen to 26 ml. of blood per kg. of body weight were then removed. Sixty to 120 minutes later another sample of blood was removed for analyses, the animal sacrificed by asphyxia and the tissues of various organs analyzed for sulfocyanide. The experimental findings were inconsistent with the concept which attributes blood dilution to the movement of a lymph-like fluid from interstitial spaces into the blood stream. The volume of sulfocyanide available water increased after hemorrhage. The chloride concentration of serum water decreased in all experiments save one. The total water and sulfocyanide available water content of cardiac muscle, pancreas, pylorus, duodenum, colon, skin and liver increased after hemorrhage. No significant differences were found in the gastrocnemius muscle and diaphragm.

WILLIAMS.

Hubbard, J. P., Preston, W. N., and Ross, R. A.: The Velocity of Blood Flow in Infants and Young Children, Determined by Radioactive Sodium. J. Clin. Investigation 21: 613, 1942.

The velocity of the blood flow in young infants and children has been measured by determining the time elapsed between the injection of radioactive sodium into

one arm and its arrival in the opposite hand. The latter has been signaled by a Geiger counter.

By this method the rate in 22 children between 2 and 12 years was found to average 11 seconds, with a range of 5 to 17 seconds. The rate of 14 infants between 6 weeks and 22 months of age averaged 7 seconds, with a range of 3 to 12 seconds.

AUTHORS.

Lascano, E. F.: The Normal Irrigation (Blood Supply) of the Keith-Flack Node. Rev. argent. de cardio. **9**: 17, 1942.

By means of infections of colored gelatin it has been found that the node of Keith and Flack is always irrigated by a single auricular artery which may be the anterior, lateral or posterior auricular, ascendant branches of the right or left circumflex artery. The artery which irrigates the sinus node is prominent between the auricular arteries and sends to the superior vena cava a large collateral which divides into two branches: an anterior or precava and a posterior branch or retrocava which form—depending on the establishment or not of anastomosis—a ring or half ring around the lower part of the superior vena cava.

If the artery of the node is the right anterior auricular, or the right lateral running anteriorly or the left anterior, lateral or posterior, the collateral which will form the ring of half ring around the superior vena cava will reach the vein by its left lateral border (ring of left origin). If, on the other side, the collateral comes from the right lateral auricular artery running posteriorly or from the right posterior auricular artery, it will reach the vein by its right lateral border (ring of right origin). From this ring of half ring an arteriole springs which runs by the sulcus terminalis, and which appears to be the real nourishing artery of the sinus block.

Constant interauricular communications have been found of a diameter of about 50 microns. These are specially frequent around the superior vena cava, in the anterior aspect of both auricles and in the posterior aspect of the left auricle. They connect both auricular arteries, right and left and sometimes they establish communications between branches of one of the coronary arteries or even of one of the auricular arteries.

In a few cases a strong ring is formed around the cava by the free anastomosis of the two pre and retro cava branches; but smaller pericaval rings formed by anastomosis of finer collaterals of those branches is a constant finding.

AUTHOR.

Davis, H. A., Eaton, A. G., and Williamson, J.: Transfusion of Bovine Serum Albumin Into Human Beings. Proc. Soc. Exper. Biol. & Med. **49**: 96, 1942.

The effect of transfusion of bovine serum albumin into human beings was determined in 13 subjects. The serum albumin was administered by vein in amounts of 50 to 300 c.c. at a rate of 5 c.c. per minute. Preliminary cross-matching was not carried out. The blood pressure was maintained at, or rose above the initial level. Vasodepression was not observed and no reactions were noted. In view of the encouraging results, the use of bovine serum albumin as a blood substitute in human beings was discussed.

KERSHBAUM.

Prinzmetal, M., Alles, G. A., Margoles, C., Kayland, S., and Davis, D. S.: Effects on Arterial Hypertension of Heat-Inactivated Tyrosinase Preparations. Proc. Soc. Exper. Boil. & Med. **50**: 288, 1942.

Mushroom tyrosinase preparations were heated to destroy about 95 per cent of their enzymic activity. These heat-inactivated tyrosinase preparations can produce significant lowering of blood pressure and remission of other symptoms

of arterial hypertension in man. The results were as marked as those reported by others using active tyrosinase preparations, which shows that the effect is not related to the enzyme content of the preparation.

WILLIAMS.

Sapirstein, L. A., Southard, F. D., Jr., and Ogden, E.: Restoration of Blood Pressure by Renin Activator After Hemorrhage. Proc. Soc. Exper. Biol. & Med. **50**: 320, 1942.

Injection of a renin-activator preparation of ox-plasma in dogs, following hemorrhage, produced a very marked rise in blood pressure, which persisted for 20 to 120 minutes. Further injection of the activator preparation during the period of restored blood pressure produced no pressor effect, but after the pressure had fallen to lower levels, whether spontaneously or after further bleeding, renewed injection again produced an increase in blood pressure. The injected renin-activator preparation contained only one-tenth or less of the total plasma protein removed. Corresponding quantities of 10 per cent gelatin or of control plasma concentrations failed to restore the blood pressure. It is concluded that the secretion of renin in severe hemorrhage is sufficient to produce exhaustion of renin activator. The resulting failure of the reno-pressor system is followed by a fatal collapse of blood pressure which may be staved off and the blood pressure restored by replacing the exhausted activator. The possibility of improving transfusion therapy of hemorrhage and shock by fortifying the plasma with preparations of renin-activator, or of substituting small quantities of activator preparations for plasma in emergency treatment, is suggested.

WILLIAMS.

Vermeulen, C., Dragstedt, L. R., Clark, D. E., Julian, O. C., and Allen, J. G.: Effect of the Administration of Lipocaic and Cholesterol in Rabbits. Arch. Surg. **44**: 260, 1942.

Experiments were undertaken in rabbits to test the possibility that a deficiency in lipocaic production plays a role in the development of vascular disease. The administration of cholesterol orally produced a sustained, hyperlipemia, hypercholesteremia, arteriosclerosis of the aorta and accumulation of cholesterol and fat in excessive amounts in the liver and adrenal glands. The simultaneous oral administration of lipocaic in amounts up to half of the daily requirement of a dog prevents a rise in the noncholesterol fraction of the blood lipids and also the deposition of fat and cholesterol in the liver but has no effect on hypercholesteremia and arteriosclerosis caused by the oral administration of cholesterol.

KERSHBAUM.

Pettus, W. W., Geiger, A. J., and Grzebien, S. T.: Effects of Morphine on the Electrocardoigram of Man, Yale J. Biol. & Med. **14**: 493, 1942.

The authors studied the effects of morphine on the electrocardiogram in 10 normal subjects and 10 patients with coronary artery disease. Doses up to ½ grain were used hypodermically, and both limb and chest leads were taken. No striking bradycardia was generally observed, as is frequently seen in animal experiments. Shift of the pacemaker and premature beats each occurred once in these experiments. The drug did not significantly alter either the initial or final portion of the ventricular complex. It is concluded that the administration of the drug would probably not cause confusion in the electrocardiographic diagnosis of acute myocardial injury in man.

KERSHBAUM.

Myerson, A., Rinkel, M., Loman, J., and Ritvo, M.: The Prolonged Effect of Amphetamine Sulphate in Gelatin. Am. J. M. Sc. 204: 254, 1942.

The following comparative effects of amphetamine-gelatin mixture and aqueous amphetamine solution were observed:

Circulatory System: The increase in blood pressure and the corresponding decrease in pulse rate produced by amphetamine was not delayed or prolonged when the drug was dissolved in gelatin.

Gastrointestinal System: There was a definite prolongation of the characteristic effects of amphetamine sulphate (decrease in tone and peristalsis) when the drug was mixed with gelatin. This action was observed in man following roentgen ray studies, and in animals by direct observation of the gastrointestinal tract.

The delay in absorption of alcohol which follows the administration of amphetamine sulphate is definitely more marked when the drug is mixed with gelatin.

AUTHORS.

Darrow, D. C., and Miller, H. C.: The Production of Cardiac Lesions by Repeated Injections of Desoxycorticosterone Acetate. J. Clin. Investigation 21: 601, 1942.

Necrosis of the myocardial fibers and replacement by fibroblasts is produced by repeated injections of desoxycorticosterone acetate in rats. The lesions are neither aggravated by absence of pyridoxin nor prevented by liberal additions of pyridoxin to the diets. Low intake of thiamin does not aggravate the lesion. The lesions cannot be distinguished from those produced by diets low in potassium. The livers decrease in size after injections of desoxycorticosterone acetate for 10 days, but are normal in size after 4 weeks of injections.

The injection of desoxycorticosterone acetate lowers muscle potassium and raises muscle sodium. Analogous changes are not found in the liver. Low cardiac potassium was found in the heart in 2 of 4 dogs fed a diet low in potassium. Injection of desoxycorticosterone produced only suggestive lowering of cardiac potassium in a group of rats, no certain change in any of 4 cats, and no change in 1 dog. Although the heart may lose potassium under conditions leading to loss from skeletal muscle, diminution of cardiac potassium is not a regular occurrence.

The cardiac lesions produced by injections of desoxycorticosterone acetate or diets low in potassium can be prevented by addition of potassium chloride to the drinking water. Deficit of body potassium is apparently essential for the production of these lesions.

Cortical extract produced analogous changes in the muscle of the one rat.

AUTHORS.

Book Review

LA DIGITAL: By Dr. Alejandro Garretón Silva, Professor of Medicine, University of Chile. Empresa Editora Zig Zag, Santiago de Chile, 1941, 143 pages.

This booklet reviews old and recent studies on the pharmacology and clinical use of digitalis. Some North American contributions, such as the method of standardization of digitalis on man described by Gold, and the changes incorporated in the United States Pharmacopoeia XII, are not included. The book does not add anything to existing knowledge concerning digitalis, but it should be useful to Spanish practitioners, for whom it was apparently designed.

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